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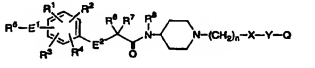

(I)

(57) Abstract

There is provided an aminophenoxyacetic acid derivative of formula (I), wherein: R^1, R^2, R^3 and R^4 are independent from each other, alkoxy group, alkyl group or aryl group, etc.; E^1 and E^2 are oxygen atom, sulfur atom, etc.; n is 0 to 5; X and Y are alkylene group, cycloalkylen group, or alkenylen group; Q is phenyl group which may be substituted or benzoyl group, etc.; or a pharmaceutically acceptable salt thereof. These compounds have neuroprotective effects by inducing calbindin D28kd, one of Ca^{2+}–binding proteins.

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DESCRIPTION

AMINOPHENOXYACETIC ACID DERIVATIVES AS NEUROPROTECTANTS

TECHNICAL FIELD

The present invention relates to novel aminophenoxyacetic acid derivatives and pharmaceutically acceptable salt thereof, which have neuroprotective effects by inducing or increasing calbindin D28Kd, one of Ca^{2+}-binding proteins, and which are useful in ameliorating and treating functional and organic disorders in the brain. More specifically, the present invention relates to therapeutic and improving agents for the allevivation or treatment of symptoms due to various ischemic disorders in the brain such as sequelae of cerebral infarction, sequelae of intracerebral hemorrhage, sequelae of cerebral arteriosclerosis and so on, and symptoms of organic brain disorder such as senile dementia, sequelae of head trauma, sequelae of surgical brain operation, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and so on.

BACKGROUND ART

It is generally considered that the pathogenesis of progressive, delayed death of nerve cells, observed in cerebral injury and cerebrovascular disease such as intracerebral hemorrhage, transient ischemia attack, and cerebral infarction, is mainly caused by a rise in intracellular Ca^{2+} concentration due to various factors related to signal transductions. Such factors related to signal transduction include, for example, abnormal activation of glutamate receptors due to excessive release glutamate, that is, an excitatory neurotransmitter, abnormal activation of ion channels, and excessive production of reactive

oxygen species/free radicals. [F. B. Meyer, *Brain Res. Rev.*, 14, 227 (1989); E. Boddeke et al., *Trends Pharmacol. Sci.*, 10, 397 (1989); J. M. McCall et al., *Ann. Rep. Med. Chem.*, 27, 31 (1992)].

From these points of view, medicaments for preventing or suppressing the neuronal cell death, such as glutamate receptor antagonists, calcium channel blockers, antioxidants and so on have been developed. However, these clinically used medicaments suppress only a few pathways related to increase of the cellular Ca^{2+} concentration, and are not sufficient for preventing or suppressing the neuronal cell death.

On the contrary, calbindin D28Kd, one of Ca^{2+}-binding proteins and mainly distributed in friable site of the brain against ischemic disease, is reported to possess buffering effects for a rise in cytotoxic intracellular Ca^{2+} concentration. [A. M. Lacopino et al., *Neurodegeneration*, 3, 1 (1994); M. P. Mattson et al., *Neuron*, 6, 41 (1991)]

Accordingly, it is expected to achieve sufficient neuroprotective effects against the increase of intracellular Ca^{2+} concentration caused by any kinds of pathways if calbindin D28Kd, one of the Ca^{2+}-binding proteins per se, can be supplied in a living body. That is, it is expected that medicaments containing calbindin D28Kd would be effective therapeutic and improving agents for the allevivation or treatment of symptoms due to various ischemic disorders in the brain such as sequelae of cerebral infarction, sequelae of intracerebral hemorrhage, sequelae of cerebral arteriosclerosis and so on, and symptoms of organic brain disorder such as senile dementia, sequelae of head trauma, sequelae of surgical brain operation, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and so on.

However, because calbindin D28Kd is unstable macromolecular protein having 28 Kd (kilo dalton) of molecular

weight, it is difficult to be administered directly into a site in the central nervous system of a living body in view of pharmacological and pharmaceutical standpoints.

On the other hand, the lower molecular compounds having effect on induction of the calbindin D28Kd can be easily prepared into the various kinds of pharmaceutical compositions by the conventional techniques. Thus, these lower molecular compounds are expected to induce the calbindin D28Kd after administration in to a body, and to possess buffering action against the increase of the cellular Ca^{2+} concentration. That is, these lower compounds can be effective compounds for improving and treating cerebral functional and organic disorders.

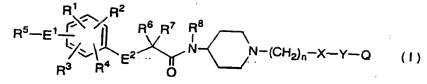
Under these circumstances, the objective of the present invention is to provide the lower molecular weight compounds having neuroprotective effect by inducing the calbindin D28Kd, one of Ca^{2+}-binding proteins, of low toxicity in suitable preparations of pharmaceutical compositions such as intravenous injectable solution.

The further purpose of the present invention is to provide the therapeutic and improving agents for the allevivation or treatment of symptoms due to various ischemic disorders in the brain such as sequelae of cerebral infarction, sequelae of intracerebral hemorrhage, sequelae of cerebral arteriosclerosis and so on, and symptoms of organic brain disorder such as senile dementia, sequelae of head trauma, sequelae of surgical brain operation, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and so on.

DISCLOSURE OF THE INVENTION

As one aspect of the present invention, it is provided aminophenoxyacetic acid derivatives represented by the following

formula (I):



(I)

wherein:

R^1, R^2, R^3 and R^4 are, independent from each other, hydrogen atom; halogen atom; hydroxy group; alkoxy group which may be substituted; alkyl group which may be substituted; aryl group which may be substituted; or aralkyl group which may be substituted;

R^5, R^6, R^7 and R^8 are, independent from each other, hydrogen atom; alkyl group which may be substituted; aryl group which may be substituted; or aralkyl group which may be substituted;

E^1 is oxygen atom; sulfur atom; or group $-NR^9-$ (in which, R^9 is hydrogen atom; alkyl group which may be substituted; aryl group which may be substituted; or aralkyl group which may be substituted);

E^2 is oxygen atom; sulfur atom; or group $-NR^{10}-$ (in which, R^{10} is hydrogen atom; alkyl group which may be substituted; aryl group which may be substituted; or aralkyl group which may be substituted);

n is 0 to 5 (provided that n=0, one of the groups of X and Y may be connecting bond but both of the groups of X and Y do not represent connecting bond at the same time);

X and Y are, independent from each other, connecting bond; alkylene group which may be substituted by hydroxyl group; cyclo-alkylene group; alkenylene group which may be substituted by lower alkyl group; -NHCO-; -CONH- or $-SO_2-$;

Q is hydrogen atom; phenyl group which may be substituted;

phenoxy group which may be substituted; benzoyl group which may be substituted; pyridyl group which may be substituted; quinolyl group which may be substituted; isoquinolyl group which may be substituted; or benzimidazolyl group which may be substituted; (provided that one of E^1 and E^2 represent either oxygen atom or sulphur atom then the other one of E^1 and E^2 represent neither oxygen atom nor sulfur atom at the same time, and in the case of E^1 is nitrogen atom and E^2 is oxygen atom, or in the case of E^1 is oxygen atom and E^2 is nitrogen atom, all of the groups of R^1, R^2, R^3 and R^4 do not represent methyl group at the same time), or pharmaceutically acceptable salts thereof.

More specifically, the present invention provides the aminophenoxyacetic acid derivatives of the formula (I), in which;

1. R^1, R^2, R^3 and R^4 are, independent from each other, hydrogen atom; halogen atom; alkoxy group; or alkyl group which may be substituted; R^5 is hydrogen atom or alkyl group which may be substituted; E^1 is -NH-; and E^2 is oxygen atom,
2. E^1 is -NH-; E^2 is oxygen atom; either the case in which X is connecting bond and Y is group -CONH-, or the other in which X is the group -CONH- and Y is connecting bond ; Q is phenyl group which may be substituted, and
3. E^1 and E^2 are -NH-; X and Y are connecting bond; Q is phenyl group which may be substituted,

or pharmaceutically acceptable salts thereof.

According to the present inventor's investigations, it is confirmed that the aminophenoxyacetic acid in low concentration represented by the formula (I) effectively induced the calbindin D28Kd and possessed excellent neuroprotective effect accordingly. Further, these compounds are also confirmed to have high safety margin, and are suitable for preparation of various kinds of

pharmaceutical compositions.

Therefore, the present invention provides the calbindin D28Kd, inducing agent containing aminophenoxyacetic acid derivatives represented by the formula (I) or pharmaceutically acceptable salts thereof as an active ingredient, as another embodiment.

As still a further embodiment, the present invention provides an improving and therapeutic agent for the cerebral functional and organic disorders containing aminophenoxyacetic acid derivatives represented by the formula (I) or pharmaceutically acceptable salt thereof, as an active ingredient.

Although lower molecular weight compounds, the aminophenoxyacetic acid derivatives of the formula (I) express the neuroprotective effect by inducing the calbindin D28Kd after administration into a living body.

Accordingly, as still another embodiment, the present invention provides a method for selecting a neuroprotective compound by measurement of inducing capability of calbindin D28Kd, which is Ca^{2+}-binding protein.

As still another embodiment, the present invention provides neuroprotective compounds to induce the calbindin D28Kd, one of Ca^{2+}-binding proteins.

As still a further embodiment, the present invention provides therapeutic and improving agents containing compounds having neuroprotective effect by inducing the calbindin D28Kd, against cerebral function disorders due to various ischemic disorders such as cerebral infarction, intracerebral hemorrhage and cerebral arteriosclerosis.

As still a further embodiment, the present invention provides therapeutic and improving agents containing compounds having neuroprotective effect by inducing calbindin D28Kd, for

cerebral organic disorders such as senile dementia, cerebral injury, sequela of cerebral surgical operation, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.

As a preferred embodiment, the present invention provides the aminophenoxyacetic acid derivatives represented by the formula (I) or pharmaceutically acceptable salt thereof is the pharmaceutical composition containing the compounds having neuroprotective effect by inducing the calbindin D28Kd.

BEST MODE FOR CARRYING OUT THE INVENTION

The aminophenoxyacetic acid derivatives of the present invention include aminophenoxyacetic acids, aminoanilinoacetic acids, aminothiophenoxyacetic acids, oxyanilinoacetic acids and thioanilinoacetic acids. Therefore, "aminophenoxyacetic acid derivatives" in this specification include all the derivatives stated above as long as not stated otherwise.

In the aminophenoxyacetic acid derivatives of the formula (I) provided by the present invention with reference to various substitution group of R^1 to R^{10}, "halogen atom" includes fluorine atom, chlorine atom and bromine atom.

The term "alkoxy group" stands for a straight-chained or branched-chained C_1-C_5 alkoxy group, and may include, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy and the like.

The term "alkyl group which may be substituted" stands for a straight-chained or branched-chained C_1-C_5 alkyl group which may be halogen-substituted, and may include, for example, methyl, ethyl, propyl, trifluoromethyl group, and the like.

The "aryl", a part of the term "aryl group which may be substituted", stands for C_4-C_{14} aryl group or heteroaryl group which may contain one or more of hetero ring atom(s) such as

nitrogen and oxygen atom(s). Examples of the preferred "aryl" include phenyl, pyridyl and naphthyl. The suitable substituents of said aryl group include halogen atom such as fluorine atom, chlorine atom and bromine atom; hydroxy group; a straight-chained or branched-chained C_1-C_5 alkoxy group such as methoxy and ethoxy group; and a straight-chained or branched-chained C_1-C_5 alkyl group which can be substituted by halogen atom such as methyl, ethyl, propyl and trifluoromethyl.

The "aralkyl", a part of the term "aralkyl group which may be substituted", stands for C_5-C_{12} aralkyl group or heteroarylalkyl group, which may contain one or more of hetero ring atom such as nitrogen and oxygen atom(s). The examples include benzyl, phenethyl, pyridylmethyl, and pyridylethyl. The suitable substituents of said aralkyl group include halogen atoms such as fluorine atom, chlorine atom and bromine atom; hydroxy group; a straight-chained or branched-chained C_1-C_5 alkoxy group such as ethoxy group; and a straight-chained or branched-chained C_1-C_5 alkyl group which may be substituted by halogen atom such as methyl, ethyl, propyl and trifluoromethyl.

The "alkylene", a part of the term "alkylene group which may be substituted by hydroxyl group", refers to the substituents X and Y, and preferably represents a straight-chained or branched-chained C_1-C_6 alkylene group such as methylene, methylmethylene, ethylene, trimethylene, tetramethylene, cyclopropylmethylene and the like.

The term "cycloalkylene" preferably stands for C_3-C_6 cycloalkylene and may include 1,1-cyclopropylene, 1,2-cyclopropylene, 1,1-cyclobutylene, 1,1-cyclopentylene, 1,1-cyclohexylene and the like. Among them, 1,1-cyclopropylene and 1,2-cyclopropylene are more preferable.

The "alkenylene", a part of the term "alkenylene group which may be substituted by lower alkyl group", may include C_2-C_4

alkenylene such as vinylene, and butadiene and vinylene is preferably used. The lower alkyl group, which is substituent of alkylene group, may be methyl, ethyl, propyl, isopropyl and the like.

The suitable substituents represented as "Q" for "phenyl group which may be substituted", "phenoxy group which may be substituted", "benzoyl group which may be substituted", "pyridyl group which may be substituted", "quinolyl group which may be substituted", "isoquinolyl group which may be substituted" and "benzimidazolyl group which may be substituted", may include halogen atom such as fluorine atom, chlorine atom and bromine atom; hydroxy group; a straight-chained or branched-chained C_1-C_5 alkoxy group such as methoxy, ethoxy group and so on. Furthermore, these substituents may also include a straight-chained or branched-chained C_1-C_5 alkyl group which may be substituted by halogen atom such as fluorine atom, chlorine atom and bromine atom. The examples include methyl, ethyl, propyl, trifluoromethyl and the like.

The term "connecting bond" with reference to "X" and "Y" means direct bond. Therefore, if "X" and/or "Y" are connecting bond, two adjacent substituents of "X" and/or "Y" are connected directly, and these substituents do not exist as "X" and/or "Y".

It is understood that when the aminophenoxyacetic acid derivatives of the formula (I) of the present invention exist in the isomer forms, each isomers per se, as well as the isomeric mixture, shall be included in the compounds of the present invention. Namely, the structural isomers may exist due to the substituents on the benzene ring. Furthermore, optical isomers may exist due to the asymmetric carbon atom of the hydroxy substituted "X" or "Y" of alkylene group. These isomers shall be included within the scope of the compounds of the present

invention.

The aminophenoxyacetic acid derivatives of the formula (I) include the compounds (Ia), (Ib) and (Ic) obtained by the synthetic process mentioned latter. For example, these compounds may be prepared by the following.

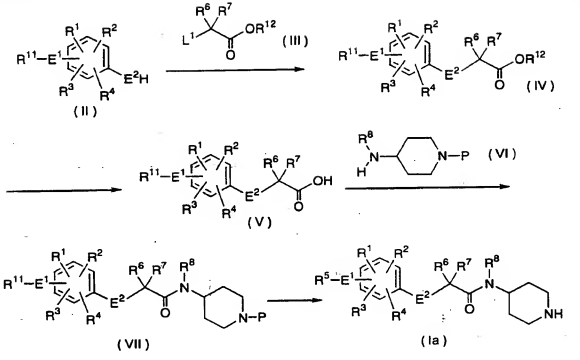
The compound (IV), obtained by the reaction of the compound (II) with the ester compound (III), is hydrolyzed to convert into carboxylic acid derivative (V). The obtained compound (V) is then converted into amide compound (VII) by the condensation reaction with the compound (VI). Further, the protecting group in the compound (VII) thus obtained is removed to obtain compound (Ia), the compound of formula (I) of the present invention, in which n is 0, X and Y is connecting bond and Q is hydrogen atom (Process 1).

The compound (Ib) can be obtained by reacting the compound (Ia) with the compound (VIII) (Process 2).

Furthermore, the compound (Ic) can be obtained by reacting the compound (Ia) with the compound (IX) (Process 3).

Each process will be further illustrated by the following reaction scheme.

Process 1:



wherein R^1 to R^8, E^1 and E^2 have the same definitions as above, and R^{11} is alkyl group which may be substituted, aryl group which may be substituted; aralkyl group which may be substituted; tert-butoxycarbonyl group; ethoxycarbonyl group; acetyl group; benzyloxycarbonyl group; p-methoxybenzyloxycarbonyl group; R^{12} is a straight-chained or branched-chained C_1-C_5 alkyl group; L^1 is leaving group which can easily be replaced with amino, hydroxy and mercapto group; P is benzyl group, tert-butoxycarbonyl group, ethoxycarbonyl group; acetyl group; benzyloxycarbonyl group; p-methoxybenzyloxycarbonyl group.

According to this process 1, the compound (Ia) can be obtained from the known starting compound (II).

Namely, for the first step, the compound (II) is reacted with 1.0 to 1.5 mole equivalent of ester compound (III) in the inert solvent, and if necessary in the presence of the base,

under stirring at -20 °C to 150 °C, preferably at 0 °C to 100 °C.

The inert solvent to be used in the reaction may be benzene, toluene, tetrahydrofuran, dioxane, dimethyformamide, dimethyl sulfoxide, acetonitrile, acetone, methanol, ethanol, isopropyl alcohol, tert-butyl alcohol, ethylene glycol and the like.

The base to be used in the above reaction may be an organic base such as triethylamine, diisopropylethylamine, pyridine and the like, or an inorganic base such as sodium, sodium hydride, potassium, potassium hydride, sodium ethoxide, potassium tert-butoxide, sodium carbonate, potassium carbonate, cesium carbonate, cesium fluoride, sodium bicarbonate, potassium bicarbonate and the like. These organic base and inorganic base may be used in combination, and sodium iodide or tetrabutylammonium iodide can be added in the reaction mixture.

The substituent "L^1" in the ester compound (III) may be the leaving group which can easily be replaced with amino, hydroxy and mercapto group, and examples include halogen atom such as chlorine atom, bromine atom, iodide atom; alkylsulfonyloxy group such as methanesulfonyloxy group; arylsulfonyloxy group such as p-toluenesulfonyloxy group, 3-nitrobenzenesulfonyloxy group and the like.

The compounds (II) and (III) to be used in this reaction are commercial available ones, or can easily prepared by the known methods.

The compound (II) and compound (III) to be used in this reaction can be commercially available and known compounds, or can be easily prepared from known compounds by using common methods.

Examples of the compound (II) include 4-(tert-butoxycarbonylamino)phenol, 4-(tert-butoxycarbonylamino)-2,3,5-trimethylphenol, 4-(tert-butoxycarbonylamino)-2-chloro-3,5,6-tri-

methylphenol, 4-(tert-butoxycarbonylamino)-2,3,6-trimethylphenol, 4-(tert-butoxycarbonylamino)-2,3-dimethylphenol, 4-(tert-butoxycarbonylamino)-2,5-dimethylphenol, 2-(tert-butoxycarbonylamino)-4,6-dimethylphenol, 5-(tert-butoxycarbonylamino)-2-methoxyphenol, 5-(tert-butoxycarbonylamino)-4-chloro-2-methoxyphenol, 4-(tert-butoxycarbonylamino)-2,6-dichlorophenol, 4-(tert-butoxycarbonylamino)-2,3,5,6-tetramethylaniline, 4-methoxy-2-methylaniline, 4-(tert-butoxycarbonylamino)-2,5,-dimethylaniline, 2-(tert-butoxycarbonylamino)-4,5-dimethylaniline, 3-(tert-butoxycarbonylamino)-2,4,6-trimethylaniline, 4-(tert-butoxycarbonylamino)-2,5-dichloroaniline, 4-(tert-butoxycarbonylamino)-2,6-dichloroaniline, 2-(tert-butoxycarbonylamino)-3,4-dichloroaniline, 4-(tert-butoxycarbonylamino)-2-methoxy-5-methylaniline, 4-(tert-butoxycarbonylamino)-2,5-dimethoxyaniline, 4-(benzyloxycarbonylamino)phenol, 4-(benzyloxycarbonylamino)-2,3,5-trimethylphenol, 4-(benzyloxycarbonylamino)-2-chloro-3,5,6-trimethylphenol, 4-(benzyloxycarbonylamino)-2,3,6-trimethylphenol, 4-(benzyloxycarbonylamino)-2,3-dimethylphenol, 4-(benzyloxycarbonylamino)-2,5-dimethylphenol, 2-(benzyloxycarbonylamino)-4,6-dimethylphenol, 5-(benzyloxycarbonylamino)-2-methoxyphenol, 5-(benzyloxycarbonylamino)-4-chloro-2-methoxyphenol, 4-(benzyloxycarbonylamino)-2,6-dichlorophenol, 4-(benzyloxycarbonylamino)-2,3,4,6-tetramethylaniline, 4-(benzyloxycarbonylamino)-2,5-dimethylaniline, 2-(benzyloxycarbonylamino)-4,5-dimethylaniline, 3-(benzyloxycarbonylamino)-2,4,6-trimethylaniline, 4-(benzyloxycarbonylamino)-2,5-dichloroaniline, 4-(benzyloxycarbonylamino)-2,6-dichloroaniline, 2-(benzyloxycarbonylamino)-3,4-dichloroaniline, 4-(benzyloxycarbonylamino)-2-methoxy-5-methylaniline, 4-(benzyloxycarbonylamino)-2,5-dimethoxyaniline and so on.

The ester compound of the formula (III) includes, for example, ethyl bromoacetate, ethyl 2-bromopropionate, ethyl 2-bromo-2-methylpropionate, and so on.

Then, the obtained compound (IV) is hydrolyzed to convert into carboxylic acid derivative (V) by the common methods, and the resultant carboxylic acid derivative of the formula (V) is further converted into amide derivative (VII) by reaction with the compound (VI).

The compound (VI) to be used for the reaction with the compound (V) is known compound as described in *J. Med. Chem.*, 36, 3707 (1993) [R. H. Mach et al.], or can be easily prepared by the methods described in EP 0184257 A1 [R. A. Stokbroekx, et al.].

The reaction conditions of this amidation reaction may vary according to the methods described in *"Compendium for Organic Synthesis"* (wiley-Interscience: A Division of John Wiley & Sons Ltd.). For example, the compound (V) is treated optionally in the presence of an organic or an inorganic base with diethyl cyanophosphonate (DEPC), diphenylphosphoryl azide (DPPA), dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide hydrochloride, 2-iodo-1-methylpyridinium iodide or benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP Reagent), and then reacted with compound (VI) to obtain the amide compound (VII). Furthermore, the compound (V) is converted into the activated ester compound such as acid halide, symmetric acid anhydride, or the mixture acid anhydride, then reacted with the compound (VI) to obtain the amide compound (VII).

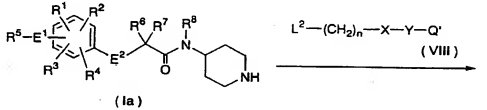
The compound (VII) thus obtained is converted into the aminophenoxyacetic acid derivatives of the formula (Ia), the compound of the present invention, by the removal reaction of the protecting group on the nitrogen atom of the amide compound (VII).

This reaction may vary depend on the protecting group on the nitrogen atom of the compound (VII). For example, the compound (VII) is treated with acids such as trifluoroacetic acid, hydrogen chloride, hydrogen bromide, or sulfuric acid in an inert

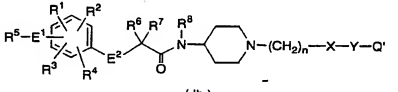
solvent such as benzene, toluene, acetonitrile, tetrahydrofuran, dioxane, chloroform, carbon tetrachloride, and the like. Furthermore, the removal of the protecting group may also be carried out by hydrogenolysis of the compound (VII) under 1 to 5 atm of hydrogen, in the presence of a catalyst such as palladium-carbon, palladium hydroxide, platinum, or platinum oxide, in an inert solvent such as methanol, ethanol, isopropyl alcohol, ethyl acetate or acetic acid.

Although each compounds obtained in the above process 1 may be used for the next reaction without further purification, it can also be used after further purification in conventional manner such as recrystallization or column chromatography and so on if necessary.

Process 2:



(Ia)



(Ib)

wherein R^1 to R^8, E^1, E^2, n, X and Y have the same definitions as above; and Q' is phenyl group which may be substituted, phenoxy group which may be substituted, benzoyl group which may be substituted, pyridyl group which may be substituted, quinolyl group which may be substituted, isoqunolyl group which may be substituted, or benzimidazolyl group which may be substituted; L^2 is leaving group which can be easily replaced with the amino

group.

According to this process 2, the aminophenoxyacetic acid of the formula (Ib) of the present invention can be obtained by reacting the compound (Ia), obtained in the process 1 mentioned above, with the compound (VIII).

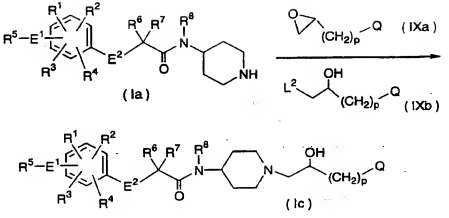
The compound (Ia) is reacted with 1.0 to 1.5 mole equivalent of the compound (VIII) in the inert solvent such as benzene, toluene, acetonitrile, ether, tetrahydrofuran, dioxan, methylene chloride, chloroform, carbon tetrachloride, dimethylformamide, and dimethyl sulfoxide in the presence of the base, at -50 °C to 120 °C, preferably at -20 °C to 50 °C.

The base to be used in the reaction may be an organic base such as triethylamine, pyridine, diisopropylethylamine and the like, or an inorganic base such as sodium carbonate, potassium carbonate, cesium carbonate, sodium bicarbonate, potassium bicarbonate, cesium fluoride, sodium hydride and the like. Sodium iodide or tetrabutylammonium iodide can be added in the reaction mixture.

The substituent "L^2" in the compound (VIII) is the leaving group, which can easily be replaced by amino group, and examples include halogen atom such as chlorine atom, bromine atom; alkylsulfonyloxy group such as methanesulfonyloxy group; arylsulfonyloxy group such as p-toluenesulfonyloxy group and the like.

In this process 2, the aminophenoxyacetic acid of the formula (Ib) can be produced as well.

Process 3:



wherein R^1 to R^8, E^1, E^2, Q and L^2 have the same definitions as previously mentioned, and p is 0 to 3.

According to this process 3, the aminophenoxyacetic acid of the formula (Ic) of the present invention can be obtained from the reaction of the compound (Ia), obtained in the process 1 mentioned above, with the compound (IXa) or the compound (IXb).

For example, the compound (Ia) is reacted with 0.9 to 1.5 mole equivalent of the compound (IXa) or (IXb) in an inert solvent at from room temperature to about 200 °C, preferably at about 50 °C to about 150 °C, to produce the aminophenoxyacetic acid of the formula (Ic).

The inert solvent to be used in the reaction may be benzene, toluene, tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, dioxane, dimethyformamide, dimethyl sulfoxide, acetonitrile, methanol, ethanol, isopropyl alcohol, t-butyl alcohol, ethylene glycol and the like.

Examples of the compound (IXa) include epibromohydrin, epichlorohydrin, (R)-epichlorohydrin, (S)-epichlorohydrin and the like, and examples of the compound (IXb) include glycidyl tosylate, (R)-glycidyl tosylate, (S)-glycidyl tosylate, (R)-

glycidyl 3-nitrobenzensulfonate, (S)-glycidyl 3-nitrobenzensulfonate, (R)-glycidyl 4-nitrobenzoate, (S)-glycidyl 4-nitrobenzoate, gylcidyltrimethylammonium chloride and the like.

In this process 3, the aminophenoxyacetic acid of the formula (Ic) can be produced as well.

The aminophenoxyacetic acid derivatives of the formula (I) thus obtained may be isolated and purified in conventional manner, such as recrystallization, column chromatography and the like.

Further, each isomers contained in the compounds of the formula (I) of the present invention can be obtained by resolution of the isomeric mixture of these compounds by the conventional methods, such as recrystallization, column chromatography, HPLC, and the like, or by using optically active reagents.

The compounds of the present invention represented by the formula (I) may be used in the form of free bases or suitable pharmaceutically acceptable acid addition salts thereof. The pharmaceutically acceptable salts can be obtained by treating the compound (I) with an inorganic acid or an organic acid in suitable solvent. Examples of the inorganic acid include hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, periodic acid and the like. Further, examples of the organic acid include formic acid, acetic acid, butyric acid, oxalic acid, malonic acid, propionic acid, valeric acid, succinic acid, fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, benzoic acid, p-toluenesulfonic acid, methanesulfonic acid and the like.

The aminophenoxyacetic acid of the present invention represented by the formula (I) or pharmaceutically acceptable

salts thereof shows low toxicity and may be administered per se. However, it may be converted in the form of pharmaceutically acceptable composition with the conventionally pharmaceutically acceptable carriers for improvement or treatment of ischemic diseases.

The dosage forms may include oral formulations such as capsules, tablets or parenteral formulations such as injection solution containing the compound of the formula (I) per se, or using the conventional excipients. For example, the capsules can be prepared by mixing the compound of the formula (I) in powder form with a suitable excipient such as lactose, starch or derivatives thereof or cellulose derivatives, and then filled in gelatin capsules.

Also, the tablets can be prepared by mixing the active ingredients with the above-mentioned excipients, binders such as sodium carboxymethylcellulose, alginic acid or gum arabic and water, then if necessary, making the resultant mixture into granules. Then, it may be further mixed with lubricant such as talc or stearic acid, and compressed into tablet by mean of common tableting machine.

Injectable formulations for parenteral route also can be prepared by dissolving the compound of the formula (I) or salts thereof in sterile distilled solution or sterile physiological saline solution with solution adjuvant, and filling it into ample. A stabilizer or buffer can be used in the injectable solution, and the injectable formulation may be administered intravenously or by dripping.

In administration of the compound of the formula (I) which possess neurocytic protecting effect based on induction of calbindin D28Kd, one of Ca^{2+}-bindind proteins, the therapeutically effective dosage for improving cerebral functional and organic disorders is not particularly limited and may vary depending on

the various kinds of factors. These factors may be the patient's condition, the severity of the disease, age, existence of a complication, administration route, formulation, as well as number of times for administration.

A usual recommended daily dose for oral administration is within the range of 0.1 - 1,000 mg/day/person, preferably 1 - 500 mg/day/person, while a usual recommended daily dose for parenteral administration is within the range of 1/100 to 1/2 based on dose of the oral administration. These doses also may vary depending on age, as well as the patient's condition.

Examples:

The present invention is illustrated in more detail by way of the following examples, but it is to be noted that the present invention is not limited by these Examples in any way.

The compound numbers in the following examples are identical to those in the Table mentioned later.

Example 1: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-methyl-N-(4-piperidinyl)acetamide (1)

A solution of 1.86 g of 2-[4-(tert-butoxycarbonylamino)-2,3,5-trimethylphenoxy]acetic acid, 1.43 g of 1-(tert-butoxycarbonyl)-4-methylaminopiperidine, 2.94 g of benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP Reagent) and 1.26 ml of triethylamine in 30 ml of dimethylformamide was stirred over night at room temperature. Then, 15 ml of saturated sodium hydrogen carbonate solution was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried and concentrated under reduced pressure to give a residue. The obtained residue was dissolved in 30 ml of methylene chloride, and to this solution was added 7.5 ml of trifluoroacetic acid at

0 °C, then the mixture was stirred for 2 hours at room temperature. After removal of the solvent, the resultant residue was purified by silica gel column chromatography (methylene chloride : methanol = 12:1) to give 1.52 g (81%) of the above-mentioned compound (1).

Example 2: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-methyl-N-(4-piperidinyl)propamide (2)

The title compound (2) was obtained from 2-[4-(tert-butoxycarbonylamino)-2,3,5-trimethylphenoxy]propionic acid and 1-(tert-butoxycarbonyl)-4-methylaminopiperidine by the same manner as the Example 1.

Example 3: 2-(4-Amino-2,3,5-trimethylphenoxy)-2-methy-N-methyl-N-(4-piperidinyl)propamide (3)

The title compound (3) was obtained from 2-[4-(tert-butoxycarbonylamino)-2,3,5-trimethylphenoxy]-2-methylpropionic acid and 1-(tert-butoxycarbonyl)-4-methylaminopiperidine by the same manner as the Example 1.

Example 4: 2-(2-Amino-4,6-dimethylphenoxy)-N-methyl-N-(4-piperidinyl)acetamide (4)

The title compound (4) was obtained from 2-[2-(tert-butoxycarbonylamino)-4,6-dimethylphenoxy]acetic acid and 1-(tert-butoxycarbonyl)-4-methylaminopiperidine by the same manner as the Example 1.

Example 5: 2-(4-Amino-2,3,6-trimethylphenoxy)-N-methyl-N-(4-piperidinyl)acetamide (5)

The title compound (5) was obtained from 2-[4-(tert-butoxycarbonylamino)-2,3,6-trimethylphenoxy]acetic acid and 1-(tert-butoxycarbonyl)-4-methylaminopiperidine by the same manner as the

Example 1.

Example 6: 2-(5-Amino-2-methoxyphenoxy)-N-methyl-N-(4-piperidinyl)acetamide (6)

The title compound (6) was obtained from 2-[5-(tert-butoxycarbonylamino)-2-methoxyphenoxy]acetic acid and 1-(tert-butoxy- carbonyl)-4-methylaminopiperidine by the same manner as the Example 1.

Example 7: 2-(5-Amino-2-methoxyphenoxy)-N-ethyl-N-(4-piperidinyl)acetamide (7)

The title compound (7) was obtained from 2-[5-(tert-butoxycarbonylamino)-2-methoxyphenoxy]acetic acid and 1-(tert-butoxycarbonyl)-4-ethylaminopiperidine by the same manner as the Example 1.

Example 8: 2-(5-Amino-4-chloro-2-methoxyphenoxy)-N-ethyl-N-(4-piperidinyl)acetamide (8)

The title compound (8) was obtained from 2-[5-(tert-butoxycarbonylamino)-4-chloro-2-methoxyphenoxy]acetic acid and 1-(tert-butoxycarbonyl)-4-ethylaminopiperidine by the same manner as the Example 1.

Example 9: 2-(4-Amino-2-chloro-3,5,6-trimethylphenoxy)-N-ethyl-N-(4-piperidinyl)acetamide (9)

The title compound (9) was obtained from 2-[4-(tert-butoxycarbonylamino)-2-chloro-3,5,6-trimethylphenoxy]acetic acid and 1-(tert-butoxycarbonyl)-4-ethylaminopiperidine by the same manner as the Example 1.

Example 10: 2-(4-Amino-2,3,5,6-tetramethylanilino)-N-methyl-N-(4-piperidinyl)acetamide (10)

The title compound (10) was obtained from 2-[4-(tert-butoxycarbonylamino)-2,3,5,6-tetramethylanilino]acetic acid and 1-(tert-butoxycarbonyl)-4-methylaminopiperidine by the same manner as the Example 1.

Example 11: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-(4-piperidinyl)acetamide (11)

The title compound (11) was obtained from 2-[4-(tert-butoxycarbonylamino)-2,3,5-trimethylphenoxy]acetic acid and 1-(tert-butoxycarbonyl)-4-aminopiperidine by the same manner as the Example 1.

Example 12: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-(4-piperidinyl)propamide (12)

The title compound (12) was obtained from 2-[4-(tert-butoxycarbonylamino)-2,3,5-trimethylphenoxy]propionic acid and 1-(tert-butoxycarbonyl)-4-aminopiperidine by the same manner as the Example 1.

Example 13: 2-(4-Amino-2,3,5-trimethylphenoxy)-2-methyl-N-(4-piperidinyl)propamide (13)

The title compound (13) was obtained from 2-[4-(tert-butoxycarbonylamino)-2,3,5-trimethylphenoxy]-2-methylpropionic acid and 1-(tert-butoxycarbonyl)-4-aminopiperidine by the same manner as the Example 1.

Example 14: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-ethyl-N-(4-piperidinyl)acetamide (14)

The title compound (14) was obtained from 2-[4-(tert-butoxycarbonylamino)-2,3,5-trimethylphenoxy]acetic acid and 1-(tert-butoxycarbonyl)-4-ethylaminopiperidine by the same manner as the Example 1.

Example 15: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-ethyl-N-(4-piperidinyl)propamide (15)

The title compound (15) was obtained from 2-[4-(tert-butoxycarbonylamino)-2,3,5-trimethylphenoxy]propionic acid and 1-(tert-butoxycarbonyl)-4-ethylaminopiperidine by the same manner as the Example 1.

Example 16: 2-(4-Amino-2-chloro-3,5,6-trimethylphenoxy)-N-methyl-N-(4-piperidinyl)acetamide (16)

The title compound (16) was obtained from 2-[4-(tert-butoxycarbonylamino)-6-chloro-2,3,5-trimethylphenoxy]acetic acid and 1-(tert-butoxycarbonyl)-4-methylaminopiperidine by the same manner as the Example 1.

Example 17: 2-(4-Amino-2-chloro-3,5,6-trimethylphenoxy)-N-(4-piperidinyl)acetamide (17)

The title compound (17) was obtained from 2-[4-(tert-butoxycarbonylamino)-6-chloro-2,3,5-trimethylphenoxy]acetic acid and 1-(tert-butoxycarbonyl)-4-aminopiperidine by the same manner as the Example 1.

Example 18: 2-(4-Amino-2,3,5,6-tetramethylanilino)-N-ethyl-N-(4-piperidinyl)acetamide (18)

The title compound (18) was obtained from 2-[4-(tert-butoxycarbonylamino)-2,3,5,6-tetramethylanilino]acetic acid and 1-(tert-butoxycarbonyl)-4-ethylaminopiperidine by the same manner as the Example 1.

Example 19: 2-(4-Amino-2,3,5,6-tetramethyl-N-methylanilino)-N-methyl-N-(4-piperidinyl)acetamide (19)

The title compound (19) was obtained from 2-[4-(tert-butoxycarbonylamino)-2,3,5,6-tetramethyl-N-methylanilino]acetic

acid and 1-(tert-butoxycarbonyl)-4-methylaminopiperidine by the same manner as the Example 1.

Example 20: 2-(4-Amino-2,3,5,6-tetramethylanilino)-N-methyl-N-(4-piperidinyl)propamide (20)

The title compound (20) was obtained from 2-[4-(tert-butoxycarbonylamino)-2,3,5,6-tetramethylanilino]propionic acid and 1-(tert-butoxycarbonyl)-4-methylaminopiperidine by the same manner as the Example 1.

Example 21: 2-[4-(Tert-butoxycarbonylamino)-2,3,5,6-tetramethylanilino]-N-(4-piperidinyl)acetamide (21)

A mixture solution of 2.2 g of 2-[4-(tert-butoxycarbonylamino)-2,3,5,6-tetramethylanilino]acetic acid, 1.67 ml of 1-benzyl-4-aminopiperidine, 10.47 g of 25% propanephosphonic acid anhydride and 4.76 ml of triethylamine in 40 ml of methylene chloride was stirred over night at room temperature. Then, 20 ml of saturated sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted with methylene chloride. The extract was washed with brine, dried and concentrated under reduced pressure to give a residue. The obtained residue was purified by silica gel column chromatography (methylene chloride : methanol = 10:1) to give 2.48 g (73%) of 2-[4-(tert-butoxycarbonylamino)-2,3,5,6-tetramethylanilino]-N-(1-benzyl-4-piperidinyl)acetamide. Then, a mixture of 438 mg of the compound obtained and 40 mg of 20%-palladium hydroxide on carbon in 4 ml of methanol was stirred for 6 hours under 5 atm of hydrogen. Then, the catalyst was filltered off a Celite (trade name) pud and the filtrate was concentrated under reduced pressure to give a residue. The obtained residue was purified by amine-coated silica gel (Fuji Silysia Chemical Ltd.; NH-DM1020) column chromatography (methylene chloride : methanol = 10:1) to

give 293 mg (81%) of the above-mentioned compound (21).

Example 22: 2-(4-Dimethylamino-2,3,5,6-tetramethylanilino)-N-methyl-N-(4-piperidinyl)acetamide (22)

The title compound (22) was obtained from 2-(4-dimethylamino-2,3,5,6-tetramethylanilino)acetic acid and 1-(tert-butoxycarbonyl)-4-methylaminopiperidine by the same manner as the Example 1.

Example 23: 2-(3-Amino-2,4,6-trimethylanilino)-N-methyl-N-(4-piperidinyl)acetamide (23)

The title compound (23) was obtained from 2-[3-(tert-butoxycarbonylamino)-2,4,6-trimethylanilino]acetic acid and 1-(tert-butoxycarbonyl)-4-methylaminopiperidine by the same manner as the Example 1.

Example 24: 2-(3-Dimethylamino-2,4,6-trimethylanilino)-N-methyl-N-(4-piperidinyl)acetamide (24)

The title compound (24) was obtained from 2-(3-dimethylamino-2,4,6-trimethylanilino)acetic acid and 1-(tert-butoxycarbonyl)-4-methylaminopiperidine by the same manner as the Example 1.

Example 25: 2-(2-Amino-4,5-dimethylanilino)-N-methyl-N-(4-piperidinyl)acetamide (25)

The title compound (25) was obtained from 2-[2-(tert-butoxycarbonylamino)-4,5-dimethylanilino]acetic acid and 1-(tert-butoxycarbonyl)-4-methylaminopiperidine by the same manner as the Example 1.

Example 26: 2-(4-Amino-2,5-dichloroanilino)-N-methyl-N-(4-piperidinyl)acetamide (26)

The title compound (26) was obtained from 2-[4-(tert-butoxycarbonylamino)-2,5-dichloroanilino]acetic acid and 1-(tert-butoxycarbonyl)-4-methylaminopiperidine by the same manner as the Example 1.

Example 27: 2-(4-Nitro-2,6-dichloroanilino)-N-methyl-N-(4-piperidinyl)acetamide (27)

The title compound (27) was obtained from 2-(4-nitro-2,6-dichloroanilino)acetic acid and 1-(tert-butoxycarbonyl)-4-methylaminopiperidine by the same manner as the Example 1.

Example 28: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-methyl-N-(1-phenethyl-4-piperidinyl)acetamide (28)

200 mg of phenethyl bromide was added to a mixture solution of 350 mg of the Compound (1) obtained in the Example 1 and 172 mg of triethylamine in 5 ml of acetonitrile, and the mixture was stirred for 5 hours at 60 °C. Then, 5 ml of saturated ammonium chloride solution was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried and concentrated under reduced pressure to give a residue. The obtained residue was purified by amine-coated silica gel (Fuji Silysia Chemical Ltd.; NH-DM1020) column chromatography (methylene chloride : methanol = 20:1) to give 390 mg (83%) of the above-mentioned compound (28).

Example 29: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-[1-(2-anilino-2-oxyethyl)-4-piperidinyl]-N-methylacetamide (29)

The title compound (29) was obtained by the same manner as the Example 28 from the Compound (1) obtained in the Example 1 and N-phenyl-2-bromoacetamide.

Example 30: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-[1-(2-anilino-2-

oxyethyl)-4-piperidinyl]-N-methylpropamide (30)

The title compound (30) was obtained by the same manner as the Example 28 from the Compound (2) obtained in the Example 2 and N-phenyl-2-bromoacetamide.

Example 31: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-methyl-N-(1-phenthyl-4-piperidinyl)propamide (31)

The title compound (31) was obtained by the same manner as the Example 28 from the Compound (2) obtained in the Example 2 and phenethyl bromide.

Example 32: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-[1-(2-(4-amino-2,3,5,6-tetramethyl)anilino-2-oxyethyl)-4-piperidinyl]-N-methyl-propamide (32)

The title compound (32) was obtained by the same manner as the Example 28 from the Compound (2) obtained in the Example 2 and N-(4-amino-2,3,5,6-tetramethyl)phenyl-2-bromoacetamide.

Example 33: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-methyl-N-[1-(2-quinolylmethyl)-4-piperidinyl]propamide (33)

The title compound (33) was obtained by the same manner as the Example 28 from the Compound (2) obtained in the Example 2 and 2-quinolylmethyl bromide.

Example 34: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-[1-(2-(4-amino-2,3,5,6-tetramethyl)anilino-2-oxyethyl)-4-piperidinyl]-N-methyl-acetamide (34)

The title compound (34) was obtained by the same manner as the Example 28 from the Compound (1) obtained in the Example 1 and N-(4-amino-2,3,5,6-tetramethyl)phenyl-2-bromoacetamide.

Example 35: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-[1-(2-

benzimidazolylmethyl)-4-piperidinyl]-N-methylpropamide (35)

The title compound (35) was obtained by the same manner as the Example 28 from the Compound (2) obtained in the Example 2 and 2-benzimidazolylmethyl bromide.

Example 36: 2-(2-Amino-4,6-dimethylphenoxy)-N-methyl-N-[1-(2-pyridylmethyl)-4-piperidinyl]acetamide (36)

The title compound (36) was obtained by the same manner as the Example 28 from the Compound (4) obtained in the Example 4 and 2-pyridylmethyl bromide.

Example 37: 2-(4-Amino-2,3,6-trimethylphenoxy)-N-methyl-N-[1-(2-phenethyl)-4-piperidinyl]acetamide (37)

The title compound (37) was obtained by the same manner as the Example 28 from the Compound (5) obtained in the Example 5 and phenethyl bromide.

Example 38: 2-(4-Amino-2,3,5-trimethylphenoxy)-2-methyl-N-methyl-N-[1-(2-phenethyl)-4-piperidinyl]propamide (38)

The title compound (38) was obtained by the same manner as the Example 28 from the Compound (3) obtained in the Example 3 and phenethyl bromide.

Example 39: 2-(4-Amino-2,3,6-trimethylphenoxy)-N-[1-(2-(4-amino-2,5-dichloroanilino)-2-oxyethyl)-4-piperidinyl]-N-methylacetamide (39)

The title compound (39) was obtained by the same manner as the Example 28 from the Compound (5) obtained in the Example 5 and N-(4-amino-2,5-dichloro)phenyl-2-bromoacetamide.

Example 40: 2-(4-Amino-2,3,5,6-tetramethylanilino)-N-methyl-N-[1-(2-phenethyl)-4-piperidinyl]acetamide (40)

The title compound (40) was obtained by the same manner as the Example 28 from the Compound (10) obtained in the Example 10 and phenethyl bromide.

Example 41: 2-(4-Amino-2,3,5,6-tetramethylanilino)-N-[1-(2-anilino-2-oxyethyl)-4-piperidinyl]-N-methylacetamide (41)

The title compound (41) was obtained by the same manner as the Example 28 from the Compound (10) obtained in the Example 10 and N-phenyl-2-bromoacetamide.

Example 42: 2-(4-Amino-2,3,5-trimethylphenoxy)-2-methyl-N-[1-(2-anilino-2-oxyethyl)-4-piperidinyl]-N-methylpropamide (42)

The title compound (42) was obtained by the same manner as the Example 28 from the Compound (3) obtained in the Example 3 and N-phenyl-2-bromoacetamide.

Example 43: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-[1-(2-(2,5-dimethyl-4-hydroxy)anilino-2-oxyethyl)-4-piperidinyl]-N-methyl-acetamide (43)

The title compound (43) was obtained by the same manner as the Example 28 from the Compound (1) obtained in the Example 1 and N-(2,5-dimethyl-4-hydroxy)phenyl-2-bromoacetamide.

Example 44: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-methyl-N-[1-(2-quinolylmethyl)-4-piperidinyl]acetamide (44)

The title compound (44) was obtained by the same manner as the Example 28 from the Compound (1) obtained in the Example 1 and 2-chloromethylquinoline.

Example 45: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-[1-(2-(3-chloro-2-methyl)anilino-2-oxyethyl)-4-piperidinyl]-N-methylacetamide (45)

The title compound (45) was obtained by the same manner as the Example 28 from the Compound (1) obtained in the Example 1 and N-(3-chloro-2-methyl)phenyl-2-bromoacetamide.

Example 46: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-[1-(2-(2-tert-butyl)anilino-2-oxyethyl)-4-piperidinyl]-N-methylacetamide (46)

The title compound (46) was obtained by the same manner as the Example 28 from the Compound (1) obtained in the Example 1 and N-(2-tert-butyl)phenyl-2-bromoacetamide.

Example 47: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-[1-(2-(2,6-dimethyl)anilino-2-oxyethyl)-4-piperidinyl]-N-methylacetamide (47)

The title compound (47) was obtained by the same manner as the Example 28 from the Compound (1) obtained in the Example 1 and N-(2,6-dimethyl)phenyl-2-bromoacetamide.

Example 48: 2-(4-Amino-2,3,5-trimethylphenoxy)-2-methyl-N-[1-(2-(3-chloro-2-methyl)anilino-2-oxyethyl)-4-piperidinyl]-N-methylpropamide (48)

The title compound (48) was obtained by the same manner as the Example 28 from the Compound (3) obtained in the Example 3 and N-(3-chloro-2-methyl)phenyl-2-bromoacetamide.

Example 49: 2-(4-Amino-2,3,5-trimethylphenoxy)-2-methyl-N-[1-(2-tert-butylanilino-2-oxyethyl)-4-piperidinyl]-N-methylpropamide (49)

The title compound (49) was obtained by the same manner as the Example 28 from the Compound (3) obtained in the Example 3 and N-(2-tert-butylmethyl)phenyl-2-bromoacetamide.

Example 50: 2-(4-Amino-2,3,5-trimethylphenoxy)-2-methyl-N-[1-(2-

(2,6-dimethyl)anilino-2-oxyethyl]-4-piperidinyl]-N-methyl-propamide (50)

The title compound (50) was obtained by the same manner as the Example 28 from the Compound (3) obtained in the Example 3 and N-(2,6-dimethyl)phenyl-2-bromoacetamide.

Example 51: 2-(5-Amino-4-chloro-2-methoxyphenoxy)-N-[1-(2-anilino-2-oxyethyl)-4-piperidinyl]-N-ethylacetamide (51)

The title compound (51) was obtained by the same manner as the Example 28 from the Compound (8) obtained in the Example 8 and N-phenyl-2-bromoacetamide.

Example 52: 2-(5-Amino-4-chloro-2-methoxyphenoxy)-N-ethyl-N-[1-(2-(2,4,6-trimethyl)anilino-2-oxyethyl)-4-piperidinyl]acetamide (52)

The title compound (52) was obtained by the same manner as the Example 28 from the Compound (8) obtained in the Example 8 and N-(2,4,6-trimethyl)phenyl-2-bromoacetamide.

Example 53: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-methyl-N-[1-(3-phenyl-2-(E)-propenyl)-4-piperidinyl]acetamide (53)

The title compound (53) was obtained by the same manner as the Example 28 from the Compound (1) obtained in the Example 1 and cinnamyl bromide.

Example 54: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-methyl-N-[1-(1-phenyl-1-cyclopropane)methyl-4-piperidinyl]acetamide (54)

The title compound (54) was obtained by the same manner as the Example 28 from the Compound (1) obtained in the Example 1 and 1-phenyl-1-cyclopropylmethyl bromide.

Example 55: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-methyl-N-[1-(2-

(1-phenylcyclopropyl)amino-2-oxyethyl-4-piperidinyl]acetamide (55)

The title compound (55) was obtained by the same manner as the Example 28 from the Compound (1) obtained in the Example 1 and N-(1-phenyl)cyclopropyl-2-bromoacetamide.

Example 56: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-methyl-N-[1-(2-phenyl-2-oxyethyl)-4-piperidinyl]acetamide (56)

The title compound (56) was obtained by the same manner as the Example 28 from the Compound (1) obtained in the Example 1 and phenacyl bromide.

Example 57: 2-(5-Amino-2-methoxyphenoxy)-N-ethyl-N-[1-(2-(2,4,6-trimethyl)anilino-2-oxyethyl)-4-piperidinyl]acetamide (57)

The title compound (57) was obtained by the same manner as the Example 28 from the Compound (7) obtained in the Example 7 and N-(2,4,6-trimethyl)phenyl-2-bromoacetamide.

Example 58: 2-(5-Amino-2-methoxyphenoxy)-N-methyl-N-[1-(2-(2,4,6-trimethyl)anilino-2-oxyethyl)-4-piperidinyl]acetamide (58)

The title compound (58) was obtained by the same manner as the Example 28 from the Compound (6) obtained in the Example 6 and N-(2,4,6-trimethyl)phenyl-2-bromoacetamide.

Example 59: 2-(5-Amino-2-methoxyphenoxy)-N-[1-(2-anilino-2-oxyethyl)-4-piperidinyl]-N-methylacetamide (59)

The title compound (59) was obtained by the same manner as the Example 28 from the Compound (6) obtained in the Example 6 and N-phenyl-2-bromoacetamide.

Example 60: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-[1-(2-(2-tert-butylanilino)-2-oxyethyl)-4-piperidinyl]-N-methylpropamide (60)

The title compound (60) was obtained by the same manner as the Example 28 from the Compound (2) obtained in the Example 2 and N-(2-tert-butyl)phenyl-2-bromoacetamide.

Example 61: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-[1-(2-(2,6-dimethylanilino)-2-oxyethyl)-4-piperidinyl]-N-methylpropamide (61)

The title compound (61) was obtained by the same manner as the Example 28 from the Compound (2) obtained in the Example 2 and N-(2,6-dimethyl)phenyl-2-bromoacetamide.

Example 62: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-methyl-N-[1-(3-phenyl-2-(E)-propenyl)-4-piperidinyl]propamide (62)

The title compound (62) was obtained by the same manner as the Example 28 from the Compound (2) obtained in the Example 2 and cinnamyl bromide.

Example 63: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-methyl-N-[1-(*trans*-2-phenyl-1-cyclopropylmethyl)-4-piperidinyl]propamide (63)

The title compound (63) was obtained by the same manner as the Example 28 from the Compound (2) obtained in the Example 2 and *trans*-2-phenyl-1-cyclopropylmethyl bromide.

Example 64: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-methyl-N-[1-(2-(1-phenylcyclopropyl)amino-2-oxyethyl)-4-piperidinyl]propamide (64)

The title compound (64) was obtained by the same manner as the Example 28 from the Compound (2) obtained in the Example 2 and N-(1-phenyl)cyclopropyl-2-bromoacetamide.

Example 65: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-methyl-N-[1-(2-hydroxy-3-phenoxy)propyl-4-piperidinyl]acetamide (65)

A mixture solution of 330 mg of Compound (1) obtained in the Example 1 and 162 mg of glycidyl phenyl ether in 8 ml of isopropanol was stirred for 4 hours at 80 °C. Then, the reaction mixture was concentrated under reduced pressure, and the resultant residue was purified by amine-coated silica gel (Fuji Silysia Chemical Ltd.; NH-DM1020) column chromatography (chloroform : methanol = 30:1) to give 266 mg (54%) of the title compound (65).

Example 66: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-methyl-N-[1-(2-*trans*-2-phenyl-1-cyclopropyl)amino-2-oxyethyl)-4-piperidinyl]acetamide (66)

The title compound (66) was obtained by the same manner as the Example 28 from the Compound (1) obtained in the Example 1 and 2-bromo-N-(*trans*-2-phenylcyclopropyl)acetamide.

Example 67: 2-(4-Amino-2,3,5-trimethylphenoxy)-2-methyl-N-methyl-N-[1-(3-phenyl-2-(E)-propenyl)-4-piperidinyl]propamide (67)

The title compound (67) was obtained by the same manner as the Example 28 from the Compound (3) obtained in the Example 3 and cinnamy bromide.

Example 68: 2-(4-Amino-2,3,5-trimethylphenoxy)-2-methyl-N-methyl-N-[1-(1-phenyl-1-cyclopropane)methyl-4-piperidinyl]propamide (68)

The title compound (68) was obtained by the same manner as the Example 28 from the Compound (3) obtained in the Example 3 and 1-phenyl-1-cyclopropylmethyl bromide.

Example 69: 2-(4-Amino-2,3,5-trimethylphenoxy)-2-methyl-N-methyl-N-[1-(2-(1-phenylcyclopropyl)amino-2-oxyethyl)-4-piperidinyl] propamide (69)

The title compound (69) was obtained by the same manner as

the Example 28 from the Compound (3) obtained in the Example 3 and N-(1-phenyl)cyclopropyl-2-bromoacetamide.

Example 70: 2-(4-Amino-2,3,5,6-tetramethylanilino)-N-methyl-N-[1-(1-phenyl-1-cyclopropane)methyl-4-piperidinyl]acetamide (70)

The title compound (70) was obtained by the same manner as the Example 28 from the Compound (10) obtained in the Example 10 and 1-phenyl-1-cyclopropylmethyl bromide.

Example 71: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-[1-(2-anilino-2-oxyethyl)-4-piperidinyl]-N-ethylacetamide (71)

The title compound (71) was obtained by the same manner as the Example 28 from the Compound (14) obtained in the Example 14 and N-phenyl-2-bromoacetamide.

Example 72: 2-(4-Amino-2-chloro-3,5,6-trimethylphenoxy)-N-methyl-N-[1-(2-(1-phenylcyclopropyl)amino-2-oxyethyl)-4-piperidinyl]-acetamide (72)

The title compound (72) was obtained by the same manner as the Example 28 from the Compound (16) obtained in the Example 16 and N-(1-phenyl)cyclopropyl-2-bromoacetamide.

Example 73: 2-(4-Amino-2-chloro-3,5,6-trimethylphenoxy)-N-[1-(2-anilino-2-oxyethyl)-4-piperidinyl]-N-ethylacetamide (73)

The title compound (73) was obtained by the same manner as the Example 28 from the Compound (9) obtained in the Example 9 and N-phenyl-2-bromoacetamide.

Example 74: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-ethyl-N-[1-(3-phenyl-2-(E)-propenyl)-4-piperidinyl]acetamide (74)

The title compound (74) was obtained by the same manner as the Example 28 from the Compound (14) obtained in the Example 14

and cinnamyl bromide.

Example 75: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-[1-(2-anilino-2-oxyethyl)-4-piperidinyl]-N-ethylpropamide (75)

The title compound (75) was obtained by the same manner as the Example 28 from the Compound (15) obtained in the Example 15 and N-phenyl-2-bromoacetamide.

Example 76: 2-(4-Amino-2,3,5,6-tetramethylanilino)-N-ethyl-N-[1-(2-phenethyl)-4-piperidinyl]acetamide (76)

The title compound (76) was obtained by the same manner as the Example 28 from the Compound (18) obtained in the Example 18 and phenethyl bromide.

Example 77: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-ethyl-N-[1-(3-phenyl-2-(E)-propenyl)-4-piperidinyl]propamide (77)

The title compound (77) was obtained by the same manner as the Example 28 from the Compound (15) obtained in the Example 15 and cinnamyl bromide.

Example 78: 2-(4-Amino-2,3,5,6-tetramethylanilino)-N-ethyl-N-[1-(3-phenyl-2-(E)-propenyl)-4-piperidinyl]acetamide (78)

The title compound (78) was obtained by the same manner as the Example 28 from the Compound (18) obtained in the Example 18 and cinnamyl bromide.

Example 79: 2-(4-Amino-2,3,5-trimethylphenoxy)-2-methyl-N-[1-(2-(4-amino-2,5-dichloro)anilino-2-oxyethyl)-4-piperidinyl]-N-methylpropamide (79)

The title compound (79) was obtained by the same manner as the Example 28 from the Compound (3) obtained in the Example 3 and N-(4-amino-2,5-dichloro)phenyl-2-bromoacetamide.

Example 80: 2-(4-Amino-2,3,5-trimethylphenoxy)-2-methyl-N-[1-(3-phenyl-2-(E)-propenyl)-4-piperidinyl]propamide (80)

The title compound (80) was obtained by the same manner as the Example 28 from the Compound (13) obtained in the Example 13 and cinnamy bromide.

Example 81: 2-(4-Amino-2,3,5-trimethylphenoxy)-2-methyl-N-[1-(1-phenyl-1-cyclopropane)methyl-4-piperidinyl]propamide (81)

The title compound (81) was obtained by the same manner as the Example 28 from the Compound (13) obtained in the Example 13 and 1-phenyl-1-cyclopropylmethyl bromide.

Example 82: 2-(4-Amino-2,3,5-trimethylphenoxy)-2-methyl-N-[1-(2-anilino-2-oxyethyl)-4-piperidinyl]propamide (82)

The title compound (82) was obtained by the same manner as the Example 28 from the Compound (13) obtained in the Example 13 and N-phenyl-2-bromoacetamide.

Example 83: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-[1-(2-anilino-2-oxyethyl)-4-piperidinyl]propamide (83)

The title compound (83) was obtained by the same manner as the Example 28 from the Compound (12) obtained in the Example 12 and N-phenyl-2-bromoacetamide.

Example 84: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-[1-(3-phenyl-2-(E)-propenyl)-4-piperidinyl]propamide (84)

The title compound (84) was obtained by the same manner as the Example 28 from the Compound (12) obtained in the Example 12 and cinnamyl bromide.

Example 85: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-[1-(2-anilino-2-oxyethyl)-4-piperidinyl]acetamide (85)

The title compound (85) was obtained by the same manner as the Example 28 from the Compound (11) obtained in the Example 11 and N-phenyl-2-bromoacetamide.

Example 86: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-[1-(3-phenyl-2-(E)-propenyl)-4-piperidinyl]acetamide (86)

The title compound (86) was obtained by the same manner as the Example 28 from the Compound (11) obtained in the Example 11 and cinnamyl bromide.

Example 87: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-ethyl-N-[1-(1-phenyl-1-cyclopropane)methyl-4-piperidinyl]propamide (87)

The title compound (87) was obtained by the same manner as the Example 28 from the Compound (15) obtained in the Example 15 and 1-phenyl-1-cyclopropylmethyl bromide.

Example 88: 2-(4-Amino-2,3,5,6-tetramethylanilino)-N-ethyl-N-[1-(1-phenyl-1-cyclopropane)methyl-4-piperidinyl]acetamide (88)

The title compound (88) was obtained by the same manner as the Example 28 from the Compound (18) obtained in the Example 18 and 1-phenyl-1-cyclopropylmethyl bromide.

Example 89: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-[1-(2-(4-amino-2,5-dichloro)anilino-2-oxyethyl)-4-piperidinyl]-N-methylacetamide (89)

The title compound (89) was obtained by the same manner as the Example 28 from the Compound (1) obtained in the Example 1 and N-(4-amino-2,5-dichloro)phenyl-2-bromoacetamide.

Example 90: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-methyl-N-[1-(1-phenyl-1-cyclopropane)methyl-4-piperidinyl]propamide (90)

The title compound (90) was obtained by the same manner as

the Example 28 from the Compound (2) obtained in the Example 2 and 1-phenyl-1-cyclopropylmethyl bromide.

Example 91: 2-(4-Amino-2-chloro-3,5,6-trimethylphenoxy)-N-[1-(2-anilino-2-oxyethyl)-4-piperidinyl]acetamide (91)

The title compound (91) was obtained by the same manner as the Example 28 from the Compound (17) obtained in the Example 17 and N-phenyl-2-bromoacetamide.

Example 92: 2-(4-Amino-2-chloro-3,5,6-trimethylphenoxy)-N-[1-(2-(4-amino-2,5-dichloro)anilino-2-oxyethyl)-4-piperidinyl]-N-methylacetamide (92)

The title compound (92) was obtained by the same manner as the Example 28 from the Compound (16) obtained in the Example 16 and N-(4-amino-2,5-dichloro)phenyl-2-bromoacetamide.

Example 93: 2-(4-Amino-2-chloro-3,5,6-trimethylphenoxy)-N-[1-(2-(2,5-dimethyl-4-hydroxy)anilino-2-oxyethyl)-4-piperidinyl]-N-ethylacetamide (93)

The title compound (93) was obtained by the same manner as the Example 28 from the Compound (9) obtained in the Example 9 and N-(2,5-dimethyl-4-hydroxy)phenyl-2-bromoacetamide.

Example 94: 2-(4-Amino-2,3,5,6-tetramethylanilino)-N-ethyl-N-[1-(*trans*-2-phenyl-1-cyclopropylmethyl)-4-piperidinyl]acetamide (94)

The title compound (94) was obtained by the same manner as the Example 28 from the Compound (18) obtained in the Example 18 and *trans*-2-phenyl-1-cyclopropylmethyl bromide.

Example 95: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-[1-(trans-2-phenyl-1-cyclopropylmethyl)-4-piperidinyl]acetamide (95)

The title compound (95) was obtained by the same manner as

the Example 28 from the Compound (11) obtained in the Example 11 and *trans*-2-phenyl-1-cyclopropylmethyl bromide.

Example 96: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-[1-(1-phenyl-1-cyclopropane)methyl-4-piperidinyl]acetamide (96)

The title compound (96) was obtained by the same manner as the Example 28 from the Compound (11) obtained in the Example 11 and 1-phenyl-1-cyclopropylmethyl bromide.

Example 97: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-(1-(2-phenethyl)-4-piperidinyl)acetamide (97)

The title compound (97) was obtained by the same manner as the Example 28 from the Compound (11) obtained in the Example 11 and phenethyl bromide.

Example 98: 2-(4-Amino-2,3,5-trimethylphenoxy)-2-methyl-N-[1-(2-(2,6-dimethylanilino)-2-oxyethyl)-4-piperidinyl]propamide (98)

The title compound (98) was obtained by the same manner as the Example 28 from the Compound (13) obtained in the Example 13 and N-(2,6-dimethylphenyl)-2-bromoacetamide.

Example 99: 2-(4-Amino-2,3,5-trimethylphenoxy)-2-methyl-N-[1-(*trans*-2-phenyl-1-cyclopropylmethyl)-4-piperidinyl]propamide (99)

The title compound (99) was obtained by the same manner as the Example 28 from the Compound (13) obtained in the Example 13 and *trans*-2-phenyl-1-cyclopropylmethyl bromide.

Example 100: 2-(4-Amino-2,3,5-trimethylphenoxy)-2-methyl-N-[1-(2-(2-tert-butylanilino)-2-oxyethyl)-4-piperidinyl]propamide (100)

The title compound (100) was obtained by the same manner as the Example 28 from the Compound (13) obtained in the Example 13 and N-(2-tert-butylphenyl)-2-bromoacetamide.

Example 101: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-[1-(1-phenyl-1-cyclopropane)methyl-4-piperidinyl]propamide (101)

The title compound (101) was obtained by the same manner as the Example 28 from the Compound (12) obtained in the Example 12 and 1-phenyl-1-cyclopropylmethyl bromide.

Example 102: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-[1-(2-(1-phenylcyclopropyl)amino-2-oxyethyl)-4-piperidinyl]propamide (102)

The title compound (102) was obtained by the same manner as the Example 28 from the Compound (12) obtained in the Example 12 and N-(1-phenyl)cyclopropyl-2-bromoacetamide.

Example 103: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-methyl-N-[1-(2-hydroxy-3-phenoxy)propyl-4-piperidinyl]propamide (103)

The title compound (103) was obtained by the same manner as the Example 65 from the Compound (2) obtained in the Example 2.

Example 104: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-[1-(2-(1-phenylcyclopropyl)amino-2-oxyethyl)-4-piperidinyl]acetamide (104)

The title compound (104) was obtained by the same manner as the Example 28 from the Compound (11) obtained in the Example 11 and N-(1-phenyl)cyclopropyl-2-bromoacetamide.

Example 105: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-methyl-N-[1-(2-(N-methylanilino)-2-oxyethyl)-4-piperidinyl]acetamide (105)

The title compound (105) was obtained by the same manner as the Example 28 from the Compound (1) obtained in the Example 1 and N-methyl-N-phenyl-2-bromoacetamide.

Example 106: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-[1-(*trans*-2-phenyl-1-cyclopropylmethyl)-4-piperidinyl]propamide (106)

The title compound (106) was obtained by the same manner

as the Example 28 from the Compound (12) obtained in the Example 12 and *trans*-2-phenyl-1-cyclopropylmethyl bromide.

Example 107: 2-(4-Amino-2,3,5-trimethylphenoxy)-2-methyl-N-[1-(2-(2,5-dimethyl-4-hydroxy)anilino-2-oxyethyl)-4-piperidinyl]-N-methylpropamide (107)

The title compound (107) was obtained by the same manner as the Example 28 from the Compound (3) obtained in the Example 3 and N-(2,5-dimethyl-4-hydroxy)phenyl-2-bromoacetamide.

Example 108: 2-(4-Amino-2,3,5-trimethylphenoxy)-N-[1-(2-(N-methylanilino)-2-oxyethyl)-4-piperidinyl]acetamide (108)

The title compound (108) was obtained by the same manner as the Example 28 from the Compound (11) obtained in the Example 11 and N-methyl-N-phenyl-2-bromoacetamide.

Example 109: 3{4-[[2-(4-Amino-2,3,5,6-tetramethylanilino)-acetyl](methyl)amino]-1-piperidino}-2-phenylpropionic acid (109)

A mixture solution of 144 mg of {4-[(tert-butoxycarbonyl)amino]-2,3,5,6-tetramethylanilino)acetic acid, 156 mg of ethyl 3-[4-(methylamino)-1-piperidino]-2-phenyl propionate, 860 mg of 25% propanephosphonic acid anhydride and 436 μl of triethylamine in 2 ml of methylene chloride was stirred over night at room temperature. Then, saturated sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted with methylene chloride. The extract was washed with brine, dried, filtrated, and concentrated under reduced pressure to give a residue. The obtained residue was purified by silica gel column chromatography (methylene chloride : methanol = 10:1) to give 180 mg (67%) of ethyl 3-{4-[({4-[(tert-butoxycarbonyl)amino]-2,3,5,6-tetramethylanilino}-acetyl)(methyl)amino]-1-piperidino}-2-phenyl propionate. Then,

178 mg of the obtained ethyl propionate was dissolved in 3 ml of 1,4-dioxane and 3 ml of 0.3N-litium hydroxide solution was added to this solution, then the mixture solution was stirred for 4 hours at room temperature. Then, the reaction mixture was acidified (pH 4) with conc. HCl solution and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried, filtrated and concentrated under reduced pressure to give a residue. Then, a mixture solution of the obtained residue in methylene chloride and trifluoroacetic acid (4:1) was stirred for 1 hour at room temperature. Then, the solvent was removed and the residue was dissolved in water and then treated with 4N-HCl solution to give 130 mg (81%) of the above-mentioned compound (109).

Example 110: 2-(4-Amino-2,3,5,6-tetramethylanilino)-N-(1-benzyl-4-piperidinyl]-N-methylacetamide (110)

The title compound (110) was obtained by the same manner as the Example 28 from the Compound (10) obtained in the Example 10 and benzyl bromide.

Example 111: 2-(4-Amino-2,3,5,6-tetramethylanilino)-N-methyl-[1-(2-phenyl-2-oxyethyl)-4-piperidinyl]acetamide (111)

The title compound (111) was obtained by the same manner as the Example 28 from the Compound (10) obtained in the Example 10 and phenacyl bromide.

Example 112: 2-(4-Amino-2,3,5,6-tetramethylanilino)-N-[1-(2-hydroxy-2-phenylethyl)-4-piperidinyl]-N-methylacetamide (112)

To a solution of the Compound (111) obtained in the Example 111 in methanol was added 1.0 equivalent of sodium borohydride at 0 °C, and the mixture was stirred for 2.5 hours at room temperature. Then, the solvent was removed and the obtained

residue was purified by amine-coated silica gel (Fuji Silysia Chemical Ltd.; NH-DM1020) column chromatography (ethyl acetate : hexane : methanol = 10:10:1) to give the above-mentioned compound (112) in 75% yield.

Example 113: 2-(4-Amino-2,3,5,6-tetramethylanilino)-N-[1-(cyclopropylmethyl)-4-piperidinyl]-N-methylacetamide (113)

The title compound (113) was obtained by the same manner as the Example 28 from the Compound (10) obtained in the Example 10 and cyclopropylmethyl bromide.

Example 114: 2-(4-Amino-2,3,5,6-tetramethylanilino)-N-methyl-N-[1-(4-pyridylmethyl)-4-piperidinyl]acetamide (114)

The title compound (114) was obtained by the same manner as the Example 28 from the Compound (10) obtained in the Example 10 and 4-picolyl chloride.

Example 115: 4-({4-[[(4-Amino-2,3,5,6-tetramethylanilino)-acetyl](methyl)amino]-1-piperidino}methyl)benzoic acid (115)

A mixture solution of the compound obtained from the Compound (10) in the Example 10 and tert-butyl 4-(bromomethyl)benzoate by the same manner as the Example 28 in 6N-HCl solution was refluxed for 2 hours. Then, the solvent was removed to give the title compound (115).

Example 116: 4-({4-[[(4-Amino-2,3,5,6-tetramethylanilino)-acetyl](methyl)amino]-1-piperidino}methyl)benzamide (116)

The title compound (116) was obtained by the same manner as the Example 28 from the Compound (10) obtained in the Example 10 and 4-bromomethylbenzamide.

Example 117: 2-(4-Amino-2,3,5,6-tetramethylanilino)-N-[1-(2-

hydroxyethyl)-4-piperidinyl]-N-methylacetamide (117)

The title compound (117) was obtained by the same manner as the Example 28 from the Compound (10) obtained in the Example 10 and 2-bromoethanol.

Example 118: 3-{4-[[(4-Amino-2,3,5,6-tetramethylanilino)-acetyl](methyl)amino]-1-piperidino}propionic acid (118)

The title compound (118) was obtained by the same manner as the Example 115 from the Compound (10) obtained in the Example 10 and tert-butyl 3-bromopropionate.

Example 119: 2-(4-Amino-2,3,5,6-tetramethylanilino)-N-methyl-N-{1-[2-(4-morpholinyl)ethyl]-4-piperidinyl}acetamide (119)

The title compound (119) was obtained by the same manner as the Example 28 from the Compound (10) obtained in the Example 10 and N-(2-bromoethyl)morpholine hydrochloride.

Example 120: 2-(4-Amino-2,3,5,6-tetramethyl-N-methylanilino)-N-methyl-N-[1-(2-phenethyl)-4-piperidinyl]acetamide (120)

The title compound (120) was obtained by the same manner as the Example 28 from the Compound (19) obtained in the Example 19 and phenethyl bromide.

Example 121: 2-(4-Amino-2,3,5,6-tetramethylanilino)-N-[1-(cyclopropylmethyl)-4-piperidinyl]-N-methylpropamide (121)

The title compound (121) was obtained by the same manner as the Example 28 from the Compound (20) obtained in the Example 20 and cyclopropylmethy bromide.

Example 122: 2-(4-Amino-2,3,5,6-tetramethylanilino)-N-methyl-N-[1-(2-phenethyl)-4-piperidinyl]propamide (122)

The title compound (122) was obtained by the same manner

as the Example 28 from the Compound (20) obtained in the Example 20 and phenethyl bromide.

Example 123: 2-(4-Amino-2,3,5,6-tetramethylanilino)-N-[1-(2-phenethyl)-4-piperidinyl]acetamide (123)

A mixture solution of the compound obtained from the Compound (21) in the Example 21 and phenethyl bromide by the same manner as the Example 28 in methylene chloride and trifluoroacetic acid (4:1) was stirred for 1 hour at 0 °C. Then, the solvent was removed to give a residue, and the obtained residue was purified by amine-coated silica gel (Fuji Silysia Chemical Ltd.; NH-DM1020) column chromatography (methylene chloride : methanol = 10:1) to give the above-mentioned compound (123) in 60% yield.

Example 124: 2-(4-Dimethylamino-2,3,5,6-tetramethylanilino)-N-methyl-N-[1-(2-phenethyl)-4-piperidinyl]acetamide (124)

The title compound (124) was obtained by the same manner as the Example 28 from the Compound (22) obtained in the Example 22 and phenethyl bromide.

Example 125: 2-(3-Amino-2,4,6-trimethylanilino)-N-methyl-N-[1-(3-phenyl-2-(E)-propenyl)-4-piperidinyl]acetamide (125)

The title compound (125) was obtained by the same manner as the Example 28 from the Compound (23) obtained in the Example 23 and cinnamyl bromide.

Example 126: 2-(3-Amino-2,4,6-tirmethylanilino)-N-[1-(2-hydroxy-3-phenoxy)propyl-4-piperidinyl]-N-methylacetamide (126)

The title compound (126) was obtained by the same manner as the Example 65 from the Compound (23) obtained in the Example 23.

Example 127: 2-(3-Amino-2,4,6-trimethylanilino)-N-methyl-N-[1-(2-phenyl-2-oxyethyl)-4-piperidinyl]acetamide (127)

The title compound (127) was obtained by the same manner as the Example 28 from the Compound (23) obtained in the Example 23 and phenacyl bromide.

Example 128: 2-(3-Amino-2,4,6-trimethylanilino)-N-(1-benzoyl-4-piperidinyl)-N-methylacetamide (128)

A mixture solution of 300 mg of the compound (23) obtained in the Example 23, 114 μl of benzoyl chloride and 206 μl of triethylamine in 5 ml of methylene chloride were stirred for 2 hoursat 0 °C. After the reaction, the solvent was removed and the obtained residue was purified by amine-coated silica gel (Fuji Silysia Chemical Ltd.; NH-DM1020) column chromatography (methylene chloride : ether = 1:1) to give the above-mentioned compound (128) in 66% yield.

Example 129: 2-(3-Amino-2,4,6-trimethylanilino)-N-[1-(cyclopropylmethyl)-4-piperidinyl]-N-methylacetamide (129)

The title compound (129) was obtained by the same manner as the Example 28 from the Compound (23) obtained in the Example 23 and cyclopropylmethyl bromide.

Example 130: 2-(3-Amino-2,4,6-trimethylanilino)-N-methyl-N-[1-(phenylsulfonyl)-4-piperidinyl]acetamide (130)

The title compound (130) was obtained by the same manner as the Example 128 from the Compound (23) obtained in the Example 23 and benzenesulfonyl chloride.

Example 131: 2-(3-Amino-2,4,6-trimethylanilino)-N-(1-benzyl-4-piperidinyl)-N-methylacetamide (131)

The title compound (131) was obtained by the same manner

as the Example 28 from the Compound (23) obtained in the Example 23 and benzyl bromide.

Example 132: 2-(3-Amino-2,4,6-trimethylanilino)-N-(1-butyl-4-piperidinyl)-N-methylacetamide (132)

The title compound (132) was obtained by the same manner as the Example 28 from the Compound (23) obtained in the Example 23 and bromobutane.

Example 133: 2-(3-Amino-2,4,6-trimethylanilino)-N-methyl-N-[1-(2-naphthyl)methyl-4-piperidinyl]acetamide (133)

The title compound (133) was obtained by the same manner as the Example 28 from the Compound (23) obtained in the Example 23 and 2-(bromomethyl)naphthalene.

Example 134: 2-(3-Amino-2,4,6-trimethylanilino)-N-methyl-N-[1-(3-trifluoromethylbenzoyl)-4-piperidinyl]acetamide (134)

The title compound (134) was obtained by the same manner as the Example 128 from the Compound (23) obtained in the Example 23 and 3-(trifluoromethyl)benzoyl chloride.

Example 135: N-(1-benzoyl-4-piperidinyl)-2-(3-dimethylamino-2,4,6-trimethylanilino)-N-methylacetamide (135)

The title compound (135) was obtained by the same manner as the Example 128 from the Compound (24) obtained in the Example 24 and benzoyl chloride.

Example 136: 2-(2-Amino-4,5-dimethylanilino)-N-methyl-N-[1-(2-phenethyl)-4-piperidinyl]acetamide (136)

The title compound (136) was obtained by the same manner as the Example 28 from the Compound (25) obtained in the Example 25 and phenethyl bromide.

Example 137: 2-(2-Amino-4,5-dimethylanilino)-N-methyl-N-[1-(*trans*-2-phenyl-1-cyclopropylmethyl)-4-piperidinyl]acetamide (137)

The title compound (137) was obtained by the same manner as the Example 28 from the Compound (25) obtained in the Example 25 and *trans*-2-phenyl-1-cyclopropylmethyl bromide.

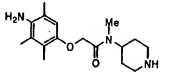
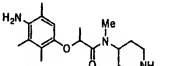
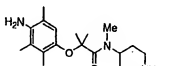
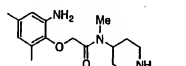
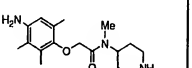
Example 138: 2-(4-Amino-2,5-dichloroanilino)-N-methyl-N-[1-(2-phenethyl)-4-piperidinyl]acetamide (138)

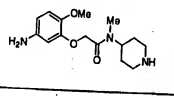
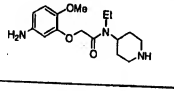
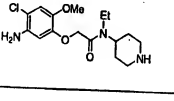
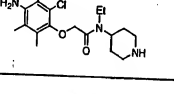
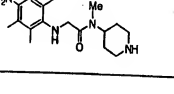
The title compound (138) was obtained by the same manner as the Example 28 from the Compound (26) obtained in the Example 26 and phenethyl bromide.

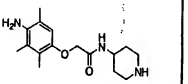
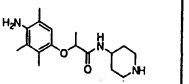
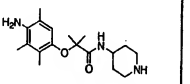
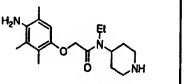
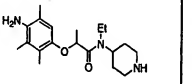
Example 139: 2-(4-Amino-2,6-dichloroanilino)-N-[1-(2-anilino-2-oxyethyl)-4-piperidinyl]-N-methylacetamide (139)

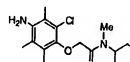
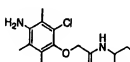
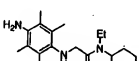
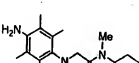
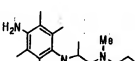
A mixture solution of the compound obtained from the compound (27) in the Example 27 and N-phenyl-2-bromoacetamide by the same manner as the Example 28 and 5% platinum sulfided on carbon in methanol and tetrahydrofuran was stirred for 3.5 hours under 4 atm of hydrogen. Then, the catalyst was removed by Celite (trade name) filtration. The obtained residue was purified by amine-coated silica gel (Fuji Silysia Chemical Ltd.; NH-DM1020) column chromatography (methylene chloride : methanol = 100:1) to give the above-mentioned compound (139) in 90% yield.

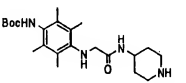
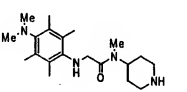
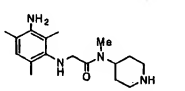
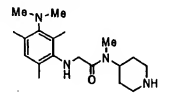
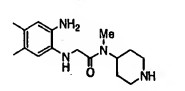
The physiochemical data of the compounds obtained by the above-mentioned examples are summarized in the following tables as Table I.

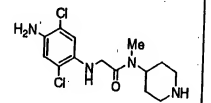
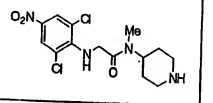
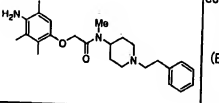
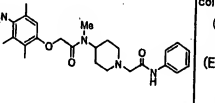
No.	Chemical Structure	Properties m. p. (°C) (solvent)	IR ($CHCl_3$) cm^{-1}	^1H-NMR ($CDCl_3$)
1		colorless cryst. (HCl salt) 191-193 (Et_2O/EtOH)	HCl salt: KBr 3424, 2940, 2805, 1642, 1489, 1418, 1321, 1298, 1284, 1140, 1100	1.46-1.80(4H, m), 2.10(3H, s), 2.15 & 2.16(3H, each s), 2.17 & 2.20(3H, each s), 2.59-2.78(2H, m), 2.87 & 2.93 (3H, each s), 3.09-3.18(2H, m), 3.34(2H, brs), 3.90 & 4.48-4.64(1H, m), 4.56 & 4.61(2H, each s), 6.55 & 6.60 (1H, each s)
2		oily substance	3019, 2935, 1624, 1484, 1420, 1377, 1320, 1251, 1137, 1110, 1087, 1035, 846	1.54(3H, d), 1.58-1.64(4H, m), 2.10(3H, s), 2.12 & 2.13(3H, each s), 2.17(3H, s), 2.56(1H, m), 2.72(1H, m), 2.82 & 2.87(3H, each s), 3.05-3.13(2H, m), 3.33(2H, brs), 4.56 & 4.55(1H, m), 4.76-4.86(1H, m), 6.46 & 6.51 (1H, each s)
3		foamy substance	3374, 2939, 1812, 1483, 1383, 1364, 1319, 1257, 1157, 1086, 1019, 804	1.35-1.75(4H, m), 1.55 & 1.56(6H, s), 2.07, 2.09, 2.14 & 2.16(9H, each s), 2.50-2.60 & 2.70-2.82(2H, m), 2.85 & 3.13 (3H, each s), 3.00-3.20(2H, m), 3.20-3.45(2H, brs), 4.55-4.85(1H, m), 6.34 & 6.39(1H, each s)
4		foamy substance	1701, 1654, 1648, 1498, 1319, 1051, 929	1.43-1.84(4H, m), 2.18(3H, s), 2.23(3H, s), 2.56-2.83 (2H, m), 2.79 & 2.90(3H, each s), 3.05-3.21(2H, m), 3.39-3.52 & 4.47-4.64(1H, m), 4.06-4.39(2H, brs), 4.50 & 4.53(2H, each s), 6.33(1H, s), 6.39(1H, s)
5		foamy substance	3394, 2953, 1654, 1484, 1417, 1320, 1225, 1090, 1052	1.60-1.91(4H, m), 2.04(3H, s), 2.17 & 2.20(6H, each s), 2.61-2.84(2H, m), 2.91(3H, s), 3.12-3.56(4H, m), 3.83 & 4.63(1H, m), 4.34 & 4.38(2H, each s), 6.25 & 6.39 (1H, each s)

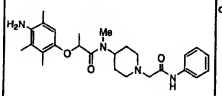
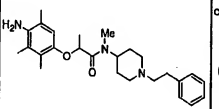
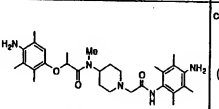
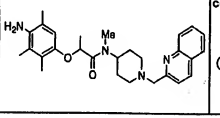
No.	Chemical Structure	Properties m. p. (°C) (solvent)	IR ($CHCl_3$) cm^{-1}	^1H-NMR ($CDCl_3$)
6		oily substance	3020, 1636, 1518, 1320, 1170, 1137, 1030, 929	1.59-1.74(4H, m), 2.67-2.75(2H, m), 2.84 & 2.95 (3H, each s), 3.10-3.13(2H, m), 3.45(2H, brs), 3.77 & 3.79(3H, each s), 4.02 & 4.52(1H, m), 4.70 & 4.73(2H, each s), 6.27(1H, m), 6.41(1H, m), 6.72(1H, m)
7		oily substance	3019, 1624, 1518, 1466, 1438, 1320, 1169, 1137, 1031, 929	1.13 & 1.22(3H, each t), 1.67-1.68(4H, m), 2.69-2.71(2H, m), 3.12(2H, m), 3.32 & 3.39(2H, each q), 3.35 & 3.97 (1H, m), 3.45(2H, brs), 3.77 & 3.79(3H, each s), 4.71(2H, s), 6.25-6.27(1H, m), 6.40 & 6.44(1H, m), 6.71(1H, m)
8		oily substance	3448, 1628, 1513, 1466, 1438, 1319, 1174, 1036, 929, 849	1.05 & 1.14(3H, each t), 1.55-1.68(4H, m), 2.56-2.75(2H, m), 3.05(2H, m), 3.20 & 3.28(2H, each q), 3.69 & 3.72 (3H, each s), 3.84 & 4.26(1H, m), 4.63(2H, s), 6.41 & 6.45(1H, each s), 6.71 & 6.73(1H, each s)
9		colorless cryst.	3020, 1629, 1466, 1436, 1380, 1320, 1087, 1037	1.21(3H, m), 1.68-1.78(4H, m), 2.08(3H, s), 2.24(3H, s), 2.27(3H, s), 2.72(2H, m), 3.15(2H, m), 3.42(2H, m), 3.55(2H, brs), 4.16-4.19(1H, m), 4.45(2H, s)
10		foamy substance	3413, 2952, 1638, 1466, 1420, 1320, 1089	1.37-1.79(4H, m), 2.12 & 2.14(6H, each s), 2.28(6H, s), 2.52-2.62 & 2.69-2.78(2H, m), 2.75 & 2.90(3H, each s), 3.08-3.18(2H, m), 3.34-3.53 & 4.61(3H, m), 3.58 & 3.63 (2H, each s)

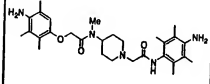
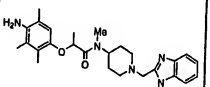
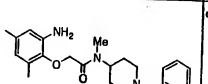
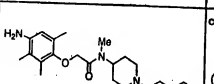
No.	Chemical Structure	Properties m. p. (℃) (solvent)	IR ($CHCl_3$) cm^{-1}	^1H-NMR ($CDCl_3$)
11		foamy substance	3416, 2931, 1670, 1530, 1485, 1444, 1320, 1253, 1122	1.30-1.44(2H, m), 1.92-2.02(2H, m), 2.12(3H, s), 2.15(3H, s), 2.18(3H, s), 2.67-2.78(2H, m), 3.07 (2H, dt), 3.39(2H, brs), 3.99(1H, m), 4.36(2H, s), 6.50(1H, s), 6.52-6.64(1H, brs)
12		foamy substance	3020, 2935, 1670, 1522, 1484, 1320, 1107	1.32-1.47(2H, m), 1.50(3H, d), 1.95(2H, m), 2.11(3H, s), 2.13(3H, s), 2.18(3H, s), 2.71-2.79 (2H, m), 3.10(2H, m), 3.39(2H, brs), 3.94(1H, m), 4.44(1H, q), 6.47(1H, s), 6.56(1H, brs)
13		foamy substance	3417, 2935, 1654, 1518, 1483, 1378, 1319, 1253, 1155, 1079, 1014, 954, 806	1.30-1.50(2H, m), 1.43(6H, s), 1.90-2.05(2H, m), 2.10(3H, s), 2.11(3H, s), 2.15(3H, s), 2.68-2.80 (2H, m), 3.05-3.15(2H, dt, J=2.4Hz, 12.7Hz), 3.30-3.60(2H, brs), 3.85-4.00(1H, m), 6.56(1H, s), 6.90(1H, brs)
14		foamy substance	3448, 1654, 1636, 1466, 1438, 1320, 1117	1.10-1.29(3H, m), 1.44-1.78(4H, m), 2.10(3H, s), 2.16(3H, s), 2.17 & 2.21(3H, each s), 2.54-2.77(2H, m), 3.08-3.18(2H, m), 3.23-3.51(4H, m), 3.89 & 4.39 (1H, m), 4.57 & 4.58(2H, each s), 6.55 & 6.60(1H, each s)
15		foamy substance	3448, 2937, 1624, 1466, 1433, 1376, 1319, 1247, 1152, 1110	1.07-1.11(3H, m), 1.52 & 1.55(3H, each d), 1.48-1.77 (4H, m), 2.09(3H, s), 2.11 & 2.12(3H, each s), 2.18(3H, s), 2.45-2.76(2H, m), 2.98-3.51(6H, m), 4.14 & 4.38 (1H, m), 4.71 & 4.80(1H, each q), 6.50 & 6.53(1H, each s)

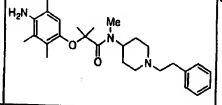
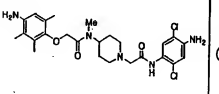
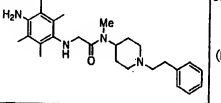
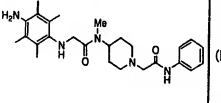
No.	Chemical Structure	Properties m. p. (°C) (solvent)	IR ($CHCl_3$) cm^{-1}	^1H-NMR ($CDCl_3$)
16		foamy substance	3008, 2951, 1632, 1464, 1418, 1320, 1086, 1050, 1033	1.61-1.76(4H, m), 2.08(3H, s), 2.24(3H, s), 2.26 (3H, s), 2.73-2.78(2H, m), 2.91 & 2.99(3H, each s), 3.14-3.16(2H, m), 3.55(2H, brs), 4.18 & 4.59(1H, m), 4.46(2H, s)
17		colorless cryst.	3408, 3018, 1668, 1623, 1534, 1417, 1320, 1108, 1089, 1045	1.45(2H, m), 1.99-2.03(2H, m), 2.08(3H, s), 2.20(3H, s), 2.24(3H, s), 2.74(2H, m), 3.10(2H, m), 3.58(2H, brs), 4.01(1H, m), 4.26(2H, s), 6.96(1H, brs)
18		foamy substance	3374, 1637, 1420, 1382, 1256, 1098	1.12-1.26(3H, m), 1.55-1.82(4H, m), 2.12 & 2.14 (6H, each s), 2.29(6H, s), 2.47-2.79(2H, m), 3.08-3.24(2H, m), 3.19 & 3.37(2H, each q), 3.28-3.53 & 4.49(3H, m), 3.60 & 3.61(2H, each s)
19		oily substance	3224, 2944, 1632, 1472, 1412, 1371, 1328, 1159, 1100, 1059	1.55(4H, m), 2.09(6H, s), 2.26(6H, s), 2.35 & 2.72-2.76 (2H, m), 2.72(3H, s), 2.84(3H, s), 3.04-3.13(2H, m), 3.51(2H, brs), 3.76 & 3.79(2H, each s), 4.58(1H, m)
20		oily substance	3004, 2952, 1628, 1458, 1412, 1320, 1224, 1208, 1139, 1086	1.20 & 1.28(3H, each d), 1.41-1.84(4H, m), 2.09 & 2.10(3H, each s), 2.11(3H, s), 2.23(3H, s), 2.25(3H, s), 2.52 & 2.73(2H, m), 2.69 & 2.77(3H, each s), 3.12(2H, m), 3.32 & 4.56(1H, m), 3.40(2H, brs), 3.94(1H, m)

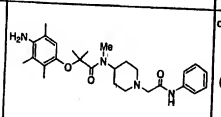
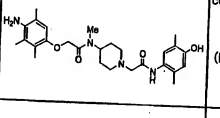
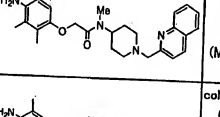
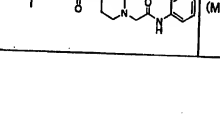
No.	Chemical Structure	Properties m. p. (℃) (solvent)	IR ($CHCl_3$) (cm^{-1})	^{1}H-NMR ($CDCl_3$)
21		foamy substance	3020, 2400, 1718, 1664, 1522, 1482, 1368, 1319, 1227, 1205, 1162	1.33-1.46(2H, m), 1.51(9H, s), 1.92-2.05(2H, m), 2.18(6H, s), 2.20(6H, s), 2.74(2H, dt), 3.09(2H, d), 3.49(2H, s), 3.50(1H, brs), 3.97(1H, m), 5.86(1H, brs), 6.99(1H, d)
22		oily substance	2924, 2779, 1640, 1450, 1407, 1370, 1329, 1285, 1064	1.50-1.80(4H, m), 2.19(6H, s), 2.24(6H, s), 2.60-2.90(2H, m), 2.76 & 2.80 & 2.89(9H, each s), 3.10-3.20(2H, m), 3.38 &4.58(1H, m), 3.67 & 3.71(2H, each s)
23		foamy substance	3020, 2101, 1654, 1648, 1482, 1438, 1407, 1225, 1207	1.52-1.79(4H, m), 2.12(3H, s), 2.17 & 2.19(3H, each s), 2.24 & 2.25(3H, each s), 2.58 & 2.73(2H, m), 2.76 & 2.89 (3H, each s), 3.08-3.20(2H, m), 3.37 & 4.59(1H, m), 3.49(2H, brs), 3.69 & 3.73(2H, each s), 4.36-4.65(1H, brs), 6.74 & 6.75(1H, each s)
24		foamy substance	3020, 2952, 1648, 1478, 1448, 1370, 1320, 1225, 1207, 1091	1.53-1.81(4H, m), 2.21(3H, s), 2.27(3H, s), 2.28(3H, s), 2.61 & 2.69-2.87(2H, m), 2.77 & 2.80(3H, each s), 2.81 (6H, s), 3.14(2H, m), 3.39 & 4.60(1H, m), 3.71 & 3.76 (2H, each s), 4.40-4.76(1H, brs), 6.78 & 6.79(1H, each s)
25		foamy substance	2944, 1641, 1582, 1408, 1288, 1243, 1154, 1107	1.63-1.81(4H, m), 2.13(3H, s), 2.17 & 2.18(3H, each s), 2.70-2.78(2H, m), 2.90 & 2.91(3H, each s), 3.16-3.22 (2H, m), 3.57 & 4.61(1H, m), 3.84 & 3.89(2H, each s), 6.43 &6.44(1H, each s), 6.54(1H, s)

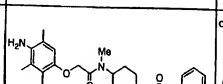
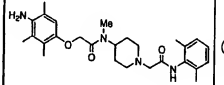
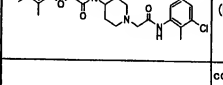
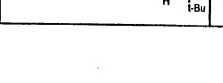
No.	Chemical Structure	Properties m. p. (℃) (solvent)	IR (KBr): cm^{-1} (HCl salt)	^{1}H-NMR ($CDCl_3$)
26		foamy substance	$CHCl_3$: free base 1654, 1648, 1522, 1508, 1458, 1420, 1225, 1206, 929	1.34-1.89(4H, m), 2.67-2.80(2H, m), 2.90 & 2.93(3H, each s), 3.09-3.27(2H, m), 3.54 & 4.60(1H, m), 3.63(2H, brs), 3.80 & 3.85(2H, each d), 5.25(1H, m), 6.51 & 6.52 (1H, each s), 6.82(1H, s)
27		foamy substance	$CHCl_3$: free base 3257, 2950, 2802, 2731, 1654, 1587, 1522, 1435, 1378, 1310, 1142, 1090	1.70-1.73(2H, m)1.78-1.88(2H, m), 2.72 & 2.81(2H, m), 2.90 &2.96(3H, each s), 3.24-3.31(2H, m), 3.41-3.52 & 4.64(1H, m), 4.44-4.49(2H, m), 6.78(1H, m), 8.14(2H, s)
28		colorless cyrst. (HCl salt) 183-185 (EtOH/Et_2O)	(KBr: $CDCl_3$) 3366, 2938, 1647, 1538, 1489, 1456, 1418, 1310, 1283, 1134, 1101, 754, 703	HCl salt (in CD_3OD) 1.88-2.09(2H, m), 2.16-2.42(2H, m), 2.23(3H, s), 2.30(3H, s), 2.37(3H, s), 2.89&3.02(3H, s), 3.07-3.23(4H, m), 3.26-3.41(2H, m), 3.67-3.84(2H, m), 4.21& 4.60(1H, m), 4.86 & 4.96(2H, each s), 6.73&6.83(1H, each s), 7.23 & 7.41(5H, m)
29		colorless cryst. (HCl salt) 177-178 (EtOH/Et_2O)	(KBr: $CDCl_3$) 2938, 1694, 1636, 1558, 1490, 1448, 1315, 1132, 1102, 948, 761	1.66-2.02(4H, m), 2.11(3H, s), 2.17&2.20(6H, each s), 2.29-2.49(2H, m), 2.85-3.05(2H, m), 2.91 & 2.99 (3H, each s), 3.14(2H, m), 3.36(2H, brs), 3.93&4.47(1H, m), 4.58&4.62(2H, each s), 6.55&6.59(1H, each s), 7.12(1H, m), 7.34(2H, m), 7.56(2H, d), 8.94&9.03(1H, brs)

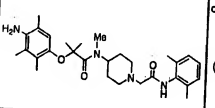
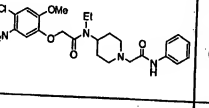
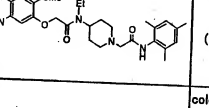
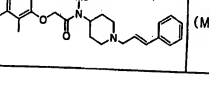
No.	Chemical Structure	Properties m. p. (℃) (solvent)	IR (KBr) : cm^{-1} (HCl salt)	^{1}H-NMR (CD_3OD): HCl salt
30		colorless cryst. (HCl salt) 191-193 ($EtOH/Et_2O$)	2938, 1694, 1624, 1600, 1557, 1490, 1448, 1315, 1113, 1074, 949, 760	free base (in $CDCl_3$) 1.38-1.97(7H, m), 2.07-2.31 & 2.36-2.49 (2H, m), 2.09 & 2.10(3H, each s), 2.13 & 2.14(3H, each s), 2.18(3H, s), 2.84-3.03(2H, m), 2.87 & 2.97(3H, each s), 3.10 & 3.13(2H, each s), 3.34(2H, brs), 4.19 & 4.48(1H, m), 4.76-4.87(1H, m), 6.46 & 6.51(1H, each s), 7.07-7.14(1H, m), 7.30-7.37(2H, m), 7.49-7.63(2H, m), 8.93 & 9.02(1H, brs)
31		colorless cryst. (HCl salt) 197-200 ($MeOH/Et_2O$)	3416, 2936, 2690, 1664, 1486, 1461, 1283, 1113, 1093, 704	1.52-1.60(3H, m), 1.84-1.97(2H, m), 2.10-2.34(2H, m), 2.21(3H, s), 2.25(3H, s), 2.30(3H, s), 2.85 & 3.06 (3H, each s), 3.03-3.23(4H, m), 3.27-3.42(2H, m), 3.69-3.78(2H, m), 4.27-4.58(1H, m), 5.07-5.22(1H, m), 6.52 & 6.59(1H, each s), 7.25-7.33(5H, m)
32		colorless cryst. (HCl salt) 220-222 ($MeOH/Et_2O$)	3442, 2937, 1634, 1538, 1486, 1456, 1284, 1112, 1034	1.53-1.63(3H, m), 1.82-1.94(2H, m), 2.16-2.39(2H, m), 2.21(6H, s), 2.22(3H, s), 2.30(3H, s), 2.31(6H, s), 2.36(3H, s), 2.86 & 3.08(3H, each s), 3.27-3.51(2H, m), 3.77(2H, m), 4.27-4.46 & 4.58(3H, m), 5.14-5.24 & 5.33-5.43(1H, m), 6.55 & 6.69(1H, each s)
33		colorless cryst. (HCl salt) 173-175 ($MeOH/Et_2O$)	3398, 2936, 1642, 1486, 1417, 1390, 1309, 1286, 1215, 1113, 1034, 836	1.54-1.63(3H, m), 1.84-1.96(2H, m), 2.23, 2.30 & 2.36 (9H, each s), 2.26-2.47(2H, m), 2.91 & 3.12(3H, s), 3.27-3.46(2H, m), 3.77-3.88(2H, m), 4.44 & 4.61(1H, m), 4.73(2H, s), 5.17-5.38(1H, m), 6.56 & 6.66(1H, s), 7.57(1H, d), 7.67(1H, m), 7.84(1H, m), 7.99(1H, d), 8.14(1H, d), 8.44(1H, d)

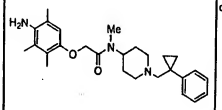
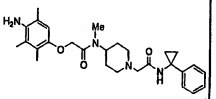
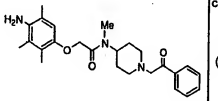
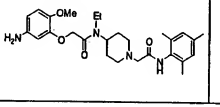
No.	Chemical Structure	Properties m. p. (°C) (solvent)	IR (KBr): cm^{-1} (HCl salt)	^{1}H-NMR (CD_3OD): HCl salt
34		colorless cryst. (HCl salt) 215-217 (MeOH/Et_2O)	3415, 2936, 1642, 1531, 1487, 1461, 1284, 1133, 1104, 950	1.91-2.10(2H, m), 2.13-2.47(2H, m), 2.21(6H, s), 2.24(3H, s), 2.30(9H, s), 2.38(3H, s), 2.89 & 3.02 (3H, each s), 3.28-3.42(2H, m), 3.76(2H, m), 4.22 & 4.61 (1H, m), 4.27-4.40(2H, m), 4.86 & 4.98(2H, each s), 6.74 & 6.85(1H, each s)
35		pale yellow cryst. (HCl salt) 153-155 (EtOH/Et_2O)	3443, 2937, 1626, 1486, 1456, 1324, 1288, 1215, 1114, 1023, 754	1.53-1.60(3H, m), 1.73-1.90(2H, m), 2.11-2.39(2H, m), 2.22(3H, s), 2.29(3H, s), 2.35(3H, s), 2.86 & 3.07(3H, each s), 2.90-3.15(2H, m), 3.45- 3.54(2H, m), 4.18-4.27 & 4.42-4.58(1H, m), 4.45 & 4.52(2H, each s), 5.18 & 5.29(1H, each q), 6.53 & 6.65(1H, each s), 7.53-7.63(2H, m), 7.73-7.83(2H, m)
36		colorless cryst. (HCl salt) 141-143 (MeOH/Et_2O)	3441, 2972, 2731, 1670, 1613, 1476, 1409, 1217, 1045, 843, 765	2.02-2.24(2H, m), 2.15 & 2.16(3H, each s), 2.20 & 2.21 (3H, esch s), 2.26-2.42(2H, m), 2.75 & 2.92(3H, each s), 3.24-3.37(2H, m), 3.46(1H, m), 3.60-3.79(2H, m), 4.51 & 4.52(2H, each s), 4.55(2H, s), 6.54(1H, s), 6.64(1H, s), 7.56(1H, dd), 7.67(1H, d), 8.02(1H, m), 8.73(1H, m)
37		colorless cryst. (HCl salt) 233-235 (MeOH/Et_2O)	2924, 2616, 1651, 1481, 1331, 1307, 1226, 1098, 1046	1.94-2.09(2H, m), 2.16-2.35(2H, m), 2.23(3H, s), 2.27(3H, s), 2.29(3H, s), 2.94(3H, s), 3.06-3.43 (6H, m), 3.68-3.83(2H, m), 4.54(2H, s), 4.64(1H, m), 7.00(1H, s), 7.22-7.39(5H, m)

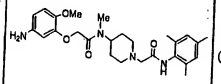
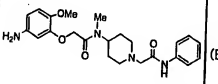
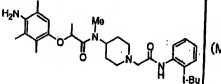
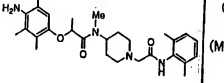
No.	Chemical Structure	Properties m. p. (℃) (solvent)	IR (KBr) : cm^{-1} (HCl salt)	^{1}H-NMR (CD_3OD): HCl salt
38		colorless cryst. (HCl salt) 163-165 (MeOH/Et_2O)	3422, 2940, 1622, 1482, 1410, 1386, 1317, 1155, 1091, 753, 703	1.63(6H, s), 1.81-1.92(2H, m), 2.11-2.36(2H, m), 2.20(3H, s), 2.29(3H, s), 2.30(3H, s), 2.88 & 3.10 (3H, each s), 2.98-3.24(4H, m), 3.27-3.38(2H, m), 3.60-3.80(2H, m), 4.61 & 4.87-4.98(1H, m), 6.45 & 6.49 (1H, each s), 7.22-7.39(5H, m)
39		colorless cryst. (HCl salt) 187-189 (MeOH/Et_2O)	3356, 3194, 2934, 1691, 1634, 1533, 1486, 1397, 1304, 1224, 1096, 950, 880	1.87-2.09(2H, m), 2.17-2.38(2H, m), 2.25(3H, s), 2.28(3H, s), 2.30(3H, s), 2.94(3H, s), 3.22-3.42(2H, m), 3.72-3.87(2H, m), 4.14(2H, s), 4.56(2H, s), 4.67 (1H, m), 6.94(1H, s), 7.07(1H, s), 7.57(1H, s)
40		colorless cryst. (HCl salt) 173-175 (MeOH/Et_2O)	3398, 2940, 2714, 1649, 1493, 1456, 1421, 1107, 1069, 951, 755, 704	free base (in $CDCl_3$) : 1.49-2.05(4H, m), 2.08-2.32(2H, m), 2.12(6H, s), 2.28(6H, s), 2.53-2.66(2H, m), 2.73-2.84 (2H, m), 2.75 & 2.90(3H, each s), 3.02-3.14(2H, m), 3.28-3.54(2H, brs), 3.34 & 4.56(1H, m), 3.59 & 3.62 (2H, each s), 7.16-7.23(3H, m), 7.24-7.32(2H, m)
41		colorless cryst. (HCl salt) 172-174 (MeOH/Et_2O)	3415, 2958, 1690, 1648, 1600, 1556, 1498, 1448, 1314, 1264, 950, 763	free base (in $CDCl_3$) : 1.48-1.98(4H, m), 2.12(6H, s), 2.28 (6H, s), 2.20-2.50(2H, m), 2.80 & 2.94(3H, each s), 3.00 (2H, m), 3.12 & 3.15(2H, each s), 3.33-3.54 & 4.56(3H, m), 3.60 & 3.63(2H, each s), 7.09-7.15(1H, m), 7.30-7.37(2H, m), 7.49-7.59(2H, m), 8.91 & 9.02(1H, brs)

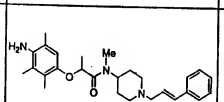
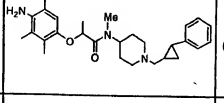
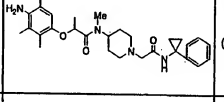
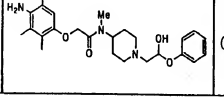
No.	Chemical Structure	Properties m. p. (℃) (solvent)	IR (KBr) : cm^{-1} (HCl salt)	^{1}H-NMR ($CDCl_3$)
42		colorless cryst. (HCl salt) 178–180 (MeOH/Et_2O)	2939, 2580, 1694, 1601, 1559, 1489, 1448, 1315, 1156, 1092, 952, 759	1.43–1.73(2H, m), 1.56(6H, s), 1.76–1.90(2H, m), 2.06 & 2.08(3H, each s), 2.09 & 2.10(3H, each s), 2.15 & 2.16 (3H, s), 2.17–2.52(2H, m), 2.83–3.04(2H, m), 2.89 & 3.18 (3H, each s), 3.08 & 3.14(2H, each s), 3.34(2H, brs), 4.55 & 4.76(1H, m), 6.32 & 6.37(1H, each s), 7.11(1H, m), 7.33(2H, m), 7.55(2H, m), 8.95 & 9.04(1H, brs)
43		colorless cryst. (HCl salt) 182–184 (MeOH/Et_2O)	3422, 3210, 2950, 1643, 1520, 1489, 1464, 1414, 1132, 1104	1.46–1.97(4H, m), 2.11(3H, s), 2.15 & 2.16(3H, each s), 2.18(3H, s), 2.20(6H, s), 2.27–2.52(2H, m), 2.82–3.07(2H, m), 2.89 & 2.95(3H, each s), 3.16(2H, s), 3.35(2H, brs), 3.94 & 4.48(1H, m), 4.58 & 4.62(2H, each s), 6.54 & 6.59(1H, each s), 6.59(1H, s), 7.55(1H, s), 8.81 & 8.89(1H, brs)
44		pale yellow cryst. (HCl salt) 174–176 (MeOH/Et_2O)	3406, 2934, 1642, 1600, 1487, 1417, 1390, 1304, 1214, 1131, 1099, 946, 842	1.53–1.70(2H, m), 1.76–2.02(2H, m), 2.07–2.36 (2H, m), 2.10(3H, s), 2.14, 2.16 & 2.19(6H, each s), 2.88 & 2.94(3H, each s), 2.92–3.04(2H, m), 3.34(2H, brs), 3.83 & 3.84(2H, each s), 3.88 & 4.50(1H, m), 4.56 & 4.61(2H, s), 6.54 & 6.59(1H, each s), 7.52(1H, m), 7.60(1H, d), 7.70 (1H, m), 7.80(1H, d), 8.07(1H, m), 8.12(1H, d)
45		colorless cryst. (HCl salt) 178–180 (MeOH/Et_2O)	3414, 2950, 1690, 1645, 1581, 1540, 1488, 1463, 1289, 1132, 1101, 1019, 950, 783	1.69–1.99(4H, m), 2.11(3H, s), 2.16 & 2.20(6H, each s), 2.30–2.56(2H, m), 2.36(3H, s), 2.89 & 2.97(3H, each s), 2.93–3.07(2H, m), 3.19(2H, s), 3.36(2H, brs), 3.96 & 4.50(1H, m), 4.58 & 4.62(2H, s), 6.55 & 6.59(1H, each s), 7.12–7.23(2H, m), 7.99(1H, m), 9.21 & 9.31(1H, brs)

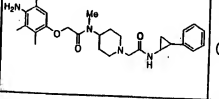
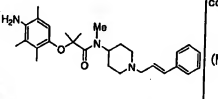
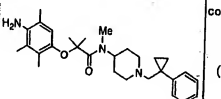
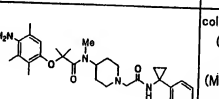
No.	Chemical Structure	Properties m. p. (°C) (solvent)	IR (KBr): cm^{-1} (HCl salt)	^{1}H-NMR ($CDCl_3$)
46		colorless cryst. (HCl salt) 186-188 ($MeOH/Et_2O$)	3416, 2964, 1684, 1646, 1534, 1488, 1292, 1131, 1101, 950, 765	1.47(9H, s), 1.65-2.00(4H, m), 2.11(3H, s), 2.15, 2.17 & 2.19(6H, each s), 2.39-2.61(2H, m), 2.85 & 2.93(3H, each s), 2.99-3.09(2H, m), 3.20(2H, s), 3.35(2H, brs), 3.95 & 4.51 (1H, m), 4.57 & 4.62(2H, each s), 6.55 & 6.59(1H, each s), 7.11(1H, m), 7.20-7.28(1H, m), 7.39(1H, m), 7.97(1H, d), 9.35 & 9.42(1H, brs)
47		colorless cryst. (HCl salt) 189-191 ($MeOH/Et_2O$)	3417, 2950, 1648, 1540, 1477, 1416, 1286, 1240, 1131, 1101, 1034, 951, 778	1.67-1.98(4H, m), 2.11(3H, s), 2.16, 2.17 & 2.20(6H, each s), 2.24(6H, s), 2.36-2.54(2H, m), 2.87 & 2.95(3H, each s), 3.04-3.16(2H, m), 3.20(2H, s), 3.36(2H, brs), 3.95 & 4.50 (1H, m), 4.58 & 4.62(2H, each s), 6.55 & 6.60(1H, each s), 7.03-7.17(3H, m), 8.54 & 8.64(1H, brs)
48		colorless cryst. (HCl salt) 172-174 ($MeOH/Et_2O$)	3402, 2944, 1695, 1616, 1582, 1540, 1464, 1404, 1292, 1156, 1092, 1016, 952, 782	1.47-1.87(4H, m), 1.56(6H, s), 2.07 & 2.08(3H, each s), 2.09 & 2.10(3H, each s), 2.15 & 2.16(3H, each s), 2.27-2.57(2H, m), 2.34(3H, s), 2.87 & 3.16(3H, each s), 2.84-3.07(2H, m), 3.13 & 3.19(2H, each s), 3.34(2H, brs), 4.60 & 4.79(1H, m), 6.32 & 6.37(1H, each s), 7.10-7.18(2H, m), 7.94-8.06(1H, m), 9.25 & 9.31(1H, brs)
49		colorless cryst. (HCl salt) 178-180 ($MeOH/Et_2O$)	3384, 2968, 1684, 1624, 1534, 1483, 1404, 1157, 1089, 952, 764	1.38-1.73(2H, m), 1.45(9H, s), 1.55 & 1.56(6H, each s), 1.77 -1.88(2H, m), 2.07 & 2.08(3H, s), 2.10(3H, s), 2.14 & 2.17 (3H, each s), 2.35 & 2.55(2H, m), 2.84 & 3.13(3H, each s), 2.90-3.09(2H, m), 3.14 & 3.20(2H, each s), 3.34(2H, brs), 4.36 & 4.78(1H, m), 6.32 & 6.36(1H, each s), 7.07-7.13 & 7.20-7.27 (2H, m), 7.38(1H, d), 7.90-8.02(1H, m), 9.38 & 9.43(1H, brs)

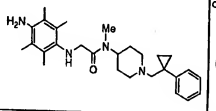
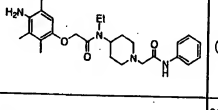
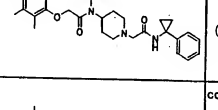
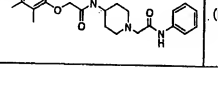
No.	Chemical Structure	Properties m. p. (℃) (solvent)	IR (KBr) : cm^{-1} (HCl salt)	^{1}H-NMR ($CDCl_3$)
50		colorless cryst. (HCl salt) 177-179 ($MeOH/Et_2O$)	2939, 2604, 1690, 1637, 1540, 1474, 1401, 1157, 1091, 951, 775	1.47-1.89(4H, m), 1.55 & 1.57(6H, each s), 2.08 & 2.10 (6H, each s), 2.14 & 2.17(3H, each s), 2.21 & 2.23(6H, each s), 2.18-2.34(1H, m), 2.50(1H, m), 2.86 & 3.15(3H, each s), 2.94-3.17(2H, m), 3.15 & 3.21(2H, each s), 3.34(2H, brs), 4.58 & 4.79(1H, m), 6.33 & 6.37(1H, s), 7.05-7.15(3H, m), 8.56 & 8.63(1H, brs)
51		colorless cryst. (HCl salt) 162-163 (iso-PrOH/ Et_2O)	3418, 2975, 1690, 1646, 1556, 1511, 1447, 1404, 1354, 1267, 1178, 1072, 948	1.20 & 1.28(3H, t), 1.65-1.95(4H, m), 2.43(2H, m), 3.02(2H, m), 3.16(2H, s), 3.30-3.50(2H, m), 3.78 & 3.81 (3H, each s), 3.97(1H, m), 4.72(2H, s), 6.51 & 6.54(1H, each s), 6.81 & 6.83(1H, each s), 7.14(1H, t), 7.36(2H, m), 7.59(2H, m), 8.97 & 9.06(1H, brs)
52		colorless cryst. (HCl salt) 172-173 (iso-PrOH/ Et_2O)	3416, 2970, 1684, 1646, 1511, 1403, 1270, 1219, 1180, 1074, 1035, 853	1.15 & 1.21(3H, each t), 1.71-1.92(4H, m), 2.21(6H, s), 2.29(3H, s), 2.45(2H, m), 3.08(2H, m), 3.21(2H, s), 3.30-3.50(2H, m), 3.78(1H, m), 3.79 & 3.80(3H, each s), 4.72(2H, brs), 6.51 & 6.55(1H, each s), 6.82(1H, s), 6.92(2H, s), 8.48 & 8.55(1H, brs)
53		colorless cryst. (HCl salt) 169-171 ($MeOH/Et_2O$)	3383, 2938, 2714, 2592, 1646, 1489, 1456, 1418, 1325, 1285, 1134, 1104, 1031, 978, 942, 749	1.47-2.26(6H, m), 2.09 & 2.10(3H, each s), 2.15, 2.17 & 2.19(6H, each s), 2.87 & 2.93(3H, each s), 3.00-3.22(4H, m), 3.33(2H, brs), 3.84 & 4.49(1H, m), 4.56 & 4.60(2H, each s), 6.16-6.36(1H, m), 6.44-6.65(2H, m), 7.18-7.40 (5H, m)

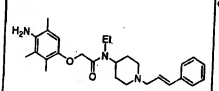
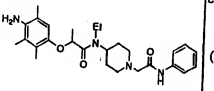
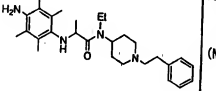
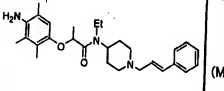
No.	Chemical Structure	Properties m. p. (℃) (solvent)	IR (KBr): cm^{-1} (HCl salt)	^{1}H-NMR ($CDCl_3$)
54		colorless cryst. (HCl salt) 166-168 (MeOH/Et_2O)	3416, 2939, 1647, 1489, 1458, 1417, 1323, 1303, 1287, 1244, 1134, 1098, 1030, 940, 704	0.64-0.77(2H, m), 0.79-0.94(2H, m), 1.44-1.82(4H, m), 1.92 -2.23(2H, m), 2.09 & 2.10(3H, each s), 2.14, 2.15 & 2.18(6H, each s), 2.54 & 2.55(2H, each s), 2.80 & 2.86(3H, each s), 2.94-3.10(2H, m), 3.35(2H, brs), 3.72 & 4.38(1H, m), 4.54 & 4.57(2H, each s), 6.52 & 6.57(1H, each s), 7.17(1H, m), 7.23-7.37(4H, m)
55		colorless cryst. (HCl salt) 188-190 (MeOH/Et_2O)	3416, 3214, 2950, 1684, 1646, 1544, 1489, 1457, 1418, 1323, 1303, 1285, 1132, 1102, 1030, 760, 700	1.23-1.33(4H, m), 1.47-1.93(4H, m), 2.10(3H, s), 2.15 & 2.19(6H, each s), 2.24(1H, m), 2.33(1H, m), 2.82-2.93 (2H, m), 2.88 & 2.95(3H, s), 2.99 & 3.00(2H, each s), 3.35(2H, brs), 3.87 & 4.42(1H, m), 4.57 & 4.60(2H, each s), 6.54 & 6.58(1H, each s), 7.15-7.33(5H, m), 7.62 & 7.68(1H, brs)
56		colorless cryst. (HCl salt) 193-195 (MeOH/Et_2O)	2942, 2860, 2593, 1694, 1642, 1597, 1488, 1451, 1306, 1260, 1230, 1132, 1102, 946	1.81-2.33(6H, m), 2.10(3H, s), 2.15, 2.17 & 2.20(6H, each s), 2.87 & 2.94(3H, each s), 3.03-3.13(2H, m), 3.81 & 3.83 (2H, each s), 3.87 & 4.51(1H, m), 4.57 & 4.61(2H, each s), 6.45 & 6.60(1H, each s), 7.46(2H, m), 7.57(1H, m), 7.98 (2H, m)
57		colorless cryst. (HCl salt) 180-184 (iso-PrOH/ Et_2O)	1646, 1515, 1486, 1445, 1400, 1166, 1138, 1020	1.14 & 1.23(3H, each t), 1.74-1.98(4H, m), 2.19(6H, s), 2.27(3H, s), 2.43(2H, m), 3.07(2H, m), 3.18(2H, s), 3.31 & 3.40(2H, each q), 3.45(2H, brs), 3.78 & 3.79(3H, each s), 4.01 & 4.16(1H, m), 4.70 & 4.72(2H, each s), 6.27 & 6.29 (1H, m), 6.40 & 6.44(1H, m), 6.71 & 6.73(1H, each s), 6.90(2H, s), 8.47 & 8.54(1H, brs)

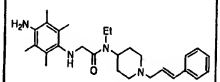
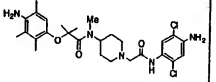
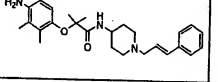
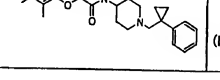
No.	Chemical Structure	Properties m. p. (℃) (solvent)	IR (KBr): cm^{-1} (HCl salt)	^{1}H-NMR ($CDCl_3$)
58		brown cryst. (HCl salt) 226-228 (EtOH/MeCN)	1645, 1515, 1446, 1350, 1296, 1166, 1139, 1061, 1023	1.67-1.92(4H, m), 2.18(6H, s), 2.27(3H, s), 2.45(2H, m), 2.85 & 2.97(3H, each s), 3.07(2H, m), 3.18(2H, s), 3.46(2H, brs), 3.78 & 3.79(3H, each s), 4.03 & 4.46(1H, m), 4.71 & 4.74(2H, s), 6.27 & 6.29(1H, each d), 6.39 & 6.42 (1H, each d), 6.72 & 6.74(1H, each s), 6.90(2H, s), 8.47 & 8.52(1H, brs)
59		colorless cryst. (HCl salt) 201-203 (EtOH/MeCN)	1694, 1646, 1599, 1557, 1515, 1447, 1166, 1139, 1061, 1021	1.69(2H, m), 1.85(2H. m), 2.42(2H, m), 2.89 & 3.01 (3H, each s), 2.97-3.01(2H, m), 3.13(2H, s), 3.45((2H, brs), 3.76 & 3.80(3H, eaoh s), 4.01 & 4.43(1H, m), 4.71 & 4.73 (2H, each s), 6.27 & 6.29(1H, m), 6.39 & 6.40(1H, m), 6.72(1H, m), 7.12(1H, d), 7.34(2H, t), 7.56(2H, d), 8.97 & 9.02(1H, brs)
60		colorless cryst. (HCl salt) 183-185 (MeOH/Et_2O)	3411, 2963, 1687, 1638, 1534, 1486, 1415, 1291, 1113, 1090, 951, 764	1.38-1.97(7H, m), 1.46(9H, s), 2.10(3H, s), 2.12 & 2.14(3H, each s), 2.17 & 2.18(3H, each s), 2.36(1H, m), 2.47-2.57 (1H, m), 2.81 & 2.92(3H, each s), 3.02(2H, m), 3.16 & 3.19 (2H, each s), 3.34(2H, brs), 4.22 & 4.52(1H, m), 4.79 & 4.83(1H, each q), 6.46 & 6.51(1H, each s), 7.11(1H, m), 7.19-7.27(1H, m), 7.38(1H, dd), 7.97(1H, d), 9.33 & 9.41 (1H,brs)
61		colorless cryst. (HCl salt) 190-192 (MeOH/Et_2O)	3424, 2942, 1688, 1634, 1538, 1478, 1416, 1286, 1240, 1113, 1074, 1035	1.41-1.98(7H, m), 2.10 & 2.11(3H, each s), 2.13 & 2.14(3H, each s), 2.17 & 2.18(3H, each s), 2.22 & 2.23(6H, each s), 2.25-2.53(2H, m), 2.83 & 2.93(3H, each s), 2.98-3.12(2H, m), 3.15-3.23(2H, m), 3.34(2H, brs), 4.23 & 4.50(1H, m), 4.80 & 4.83 (1H, each q), 6.46 & 6.52(1H, each s), 7.05-7.15(3H, m), 8.48-8.67(1H, m)

No.	Chemical Structure	Properties m. p. (℃) (solvent)	IR (KBr): cm^{-1} (HCl salt)	^{1}H-NMR ($CDCl_3$)
62		pale yellow cryst. (HCl salt) 178-180 ($MeOH/Et_2O$)	3410, 2937, 2712, 1638, 1487, 1452, 1413, 1323, 1283, 1244, 1215, 1113, 1075, 976, 749	1.25-2.03(6H, m), 1.54(3H, t), 2.09(3H, s), 2.12 & 2.13(3H, each s), 2.17 & 2.18(3H, each s), 2.82 & 2.92(3H, each s), 3.04(2H, m), 3.09-3.18(2H, m), 3.31(2H, brs), 4.11 & 4.50 (1H, m), 4.73-4.92(1H, m), 6.17-6.32(1H, m), 6.43-6.58 (2H, m), 7.22(1H, m), 7.30(2H, m), 7.37(2H, m)
63		colorless cryst. (HCl salt) 169-171 ($MeOH/Et_2O$)	3411, 2937, 1648, 1605, 1486, 1460, 1417, 1323, 1285, 1243, 1115, 1032, 759, 700	0.75-0.86(1H, m), 0.91-1.02(1H, m), 1.15-1.27(1H, m), 1.32-2.22(7H, m), 1.54(3H, t), 2.09(3H, s), 2.12 & 2.13(3H, each s), 2.14 & 2.16(3H, each s), 2.26-2.57(2H, m), 2.81 & 2.90(3H, each s), 2.98-3.16(2H, m), 3.32(2H, brs), 4.10 & 4.47(1H, m), 4.79(1H, m), 6.45 & 6.50(1H, each s), 7.03 (2H, m), 7.14(1H, m), 7.20-7.29(2H, m)
64		colorless cryst. (HCl salt) 182-185 ($MeOH/Et_2O$)	3411, 3203, 2940, 2590, 1688, 1638, 1545, 1486, 1458, 1416, 1322, 1284, 1110, 1030, 760, 700	1.19-1.33(4H, m), 1.47-1.90(7H, m), 2.07-2.38(2H, m), 2.10 (3H, s), 2.12 & 2.13(3H, each s), 2.16 & 2.17(3H, each s), 2.75-2.90(2H, m), 2.83 & 2.93(3H, each s), 2.94-3.03(2H, m), 3.34(2H, brs), 4.15 & 4.42(1H, m), 4.73-4.86(1H, m), 6.45 & 6.50(1H, each s), 7.15-7.32(5H, m), 7.59 & 7.67 (1H, brs)
65		colorless cryst. (HCl salt) 176-178 ($MeOH/Et_2O$)	3368, 2932, 2874, 2573, 1647, 1598, 1492, 1459, 1417, 1293, 1244, 1137, 1109, 1038, 757	1.47-1.98(4H, m), 2.10(3H, s), 2.15, 2.16 & 2.20(6H, each s), 2.29-2.60(4H, m), 2.84-3.12(2H, m), 2.88 & 2.94 (3H, each s), 3.34(2H, brs), 3.88 & 4.49(1H, m), 3.98(2H, d), 4.02-4.12(1H, m), 4.57 & 4.61(2H, each s), 6.54 & 6.59 (1H, each s), 6.87-7.01(3H, m), 7.24-7.32(2H, m)

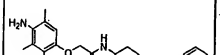
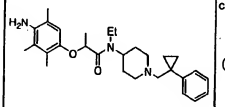
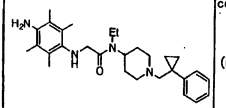
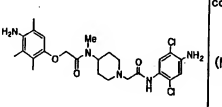
No.	Chemical Structure	Properties m. p. (℃) (solvent)	IR (KBr): cm^{-1} (HCl salt)	^{1}H-NMR ($CDCl_3$)
66		colorless cryst. (HCl salt) 186-188 ($MeOH/Et_2O$)	3392, 3214, 2590, 1672, 1556, 1487, 1461, 1415, 1286, 1131, 1103, 1031, 951, 700	1.15-1.23(2H, m), 1.25-1.32(1H, m), 1.50-1.93(4H, m), 2.06(1H, m), 2.10(3H, s), 2.15(3H, s), 2.19(3H, s), 2.24(1H, m), 2.33(1H, m), 2.81-3.06(2H, m), 2.88 & 2.96(3H, each s), 3.00(2H, s), 3.35(2H, brs), 3.88 & 4.42 (1H, m), 4.57 & 4.60(2H, each s), 6.54 & 6.58(1H, each s), 7.13-7.33(6H, m)
67		colorless cryst. (HCl salt) 178-180 ($MeOH/Et_2O$)	3982, 2939, 2586, 1618, 1482, 1410, 1156, 1096, 978, 950, 748	1.37-1.67(2H, m), 1.56(6H, s), 1.73-1.86(2H, m), 1.88-2.20(2H, m), 2.05 & 2.08(3H, s), 2.09(3H, s), 2.13 & 2.16(3H, each s), 2.85 & 3.13(3H, each s), 2.92-3.19(4H, m), 3.32(2H, brs), 4.59 & 4.70(1H, m), 6.17-6.35(1H, m), 6.33 & 6.38(1H, each s), 6.48 & 6.52(1H, each d), 7.22(1H, m), 7.30(2H, m), 7.36(2H, m)
68		colorless cryst. (HCl salt) 187-189 (iso-PrOH/ Et_2O)	3382, 2939, 2587, 1622, 1482, 1409, 1318, 1156, 1089, 1029, 763, 704	(HCl salt in CD_3OD): 1.12(4H, m), 1.43-1.77(2H, m), 1.60(6H, s), 1.99-2.15(2H, m), 2.18 & 2.19(3H, each s), 2.28(6H, s), 2.79 & 3.01(3H, each s), 2.84-3.15(2H, m), 3.46-3.66(2H, m), 3.49(2H, s), 4.52 & 4.74-4.86(1H, m), 6.41 & 6.45(1H, each s), 7.30(1H, m), 7.39(2H, m), 7.44-7.57(2H, m)
69		colorless cryst. (HCl salt) 184-186 ($MeOH/Et_2O$)	3416, 3194, 2946, 2590, 1688, 1630, 1548, 1482, 1460, 1403, 1321, 1156, 1092, 1029, 953, 759	1.19-1.32(4H, m), 1.37-1.84(10H, m), 2.03-2.20 & 2.34 (2H, m), 2.07(3H, s), 2.10(3H, s), 2.14(3H, s), 2.72-2.92 (2H, m), 2.86 & 2.95(2H, each s), 3.00 & 3.14(3H, each s), 3.34(2H, brs), 4.49 & 4.71(1H, m), 6.31 & 6.36(1H, each s), 7.15-7.32(5H, m), 7.61 & 7.68(1H, brs)

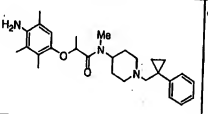
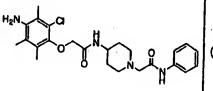
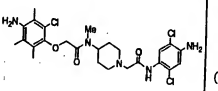
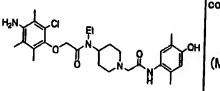
No.	Chemical Structure	Properties m. p. (℃) (solvent)	IR (KBr): cm^{-1} (HCl salt)	^1H-NMR ($CDCl_3$)
70		colorless cryst. (HCl salt) 179-181 (MeOH/Et_2O)	3381, 2947, 2731, 2588, 1649, 1582, 1496, 1450, 1417, 1104, 1065, 1030, 766, 704	(HCl salt in CD_3OD): 1.09-1.19(4H, m), 1.79-1.96(2H, m), 2.07-2.20(2H, m), 2.29, 2.31, 2.35 & 2.37(12H, each s), 2.85 & 2.90(3H, each s), 3.01-3.25(2H, m), 3.50 & 3.51 (2H, each s), 3.55-3.68(2H, m), 3.93 & 4.57(1H, m), 4.21 & 4.44(2H, each s), 7.25-7.57(5H, m)
71		colorless cryst. (HCl salt) 178-180 (MeOH/Et_2O)	3416, 2968, 2596, 1693, 1629, 1600, 1556, 1490, 1448, 1316, 1236, 1131, 1111, 1032	1.16-1.30(3H, m), 1.76(2H, m), 1.82-2.08(2H, m), 2.10(3H, s), 2.16 & 2.21(6H, each s), 2.36(2H, m), 2.99 (2H, m), 3.13(2H, s), 3.25-3.51(4H, m), 3.92 & 4.15 (1H, m), 4.58 & 4.59(2H, each s), 6.55 & 6.60(1H, each s), 7.12(1H, t), 7.34(2H, t), 7.55(2H, m), 8.93 & 9.06(1H, brs)
72		colorless cryst. (HCl salt) 180-184 (EtOH/Et_2O)	1687, 1638, 1546, 1498, 1456, 1417, 1320, 1304, 1100, 1031	1.28(4H, m), 1.70-1.92(4H, m), 2.07(3H, s), 2.24(3H, s), 2.25(3H, s), 2.34(2H, m), 2.89(2H, m), 2.92(2H, s), 3.01 & 3.02(3H, each s), 3.56(2H, brs), 4.20 & 4.50 (1H, m), 4.46(2H, s), 7.16-7.21(1H, m), 7.24-7.30 (4H, m), 7.66 & 7.70(1H, brs)
73		colorless cryst. (HCl salt) 208-210 (EtOH/Et_2O)	1692, 1634, 1556, 1500, 1448, 1411, 1317, 1106, 1050	1.25-1.27(3H, m), 1.82-2.03(4H, m), 2.08(3H, s), 2.25(3H, s), 2.26(3H, s), 2.43(2H, m), 3.01(2H, m), 3.15(2H, s), 3.41-3.45(2H, m), 3.56(2H, brs), 4.23 (1H, m), 4.45(2H, s), 7.12(1H, t), 7.34(2H, t), 7.58 (2H, d), 9.01 & 9.08(1H, brs)

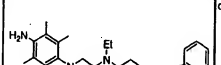
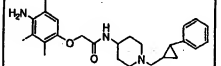
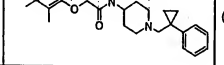
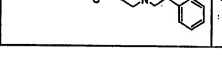
No.	Chemical Structure	Properties m. p. (℃) (solvent)	IR (KBr) : cm^{-1} (HCl salt)	^{1}H-NMR ($CDCl_3$)
74		colorless cryst. (HCl salt) 170–172 (MeOH/Et_2O)	3406, 2938, 2596, 1650, 1485, 1460, 1324, 1284, 1215, 1133, 1111, 1033, 977, 945	1.15 & 1.20(3H, m), 1.66–2.24(6H, m), 2.10(3H, s), 2.15(3H, s), 2.17 & 2.20(3H, each s), 3.05(2H, m), 3.14 (2H, m), 3.25–3.43(4H, m), 3.42 & 3.83(1H, m), 4.58(2H, s), 6.26(1H, m), 6.51(1H, m), 6.54 & 6.60 (1H, each s), 7.22(1H, t), 7.30(2H, t), 7.37(2H, d)
75		colorless cryst. (HCl salt) 173–174 (MeOH/Et_2O)	3405, 3193, 2974, 1695, 1623, 1556, 1489, 1448, 1315, 1259, 1215, 1109, 1030, 949	1.15 & 1.16(3H, each t), 1.37–1.94(7H, m), 1.95–2.44(2H, m), 2.09(3H, s), 2.13(3H, s), 2.17 & 2.18(3H, each s), 2.85–3.02(2H, m), 3.09 & 3.13(2H, each s), 3.20–3.52(4H, m), 4.05–4.24(1H, m), 4.73 & 4.80(1H, each q), 6.51 & 6.53 (1H, each s), 7.11(1H, t), 7.33(2H, t), 7.55(2H, m), 8.91 & 9.07(1H, brs)
76		colorless cryst. (HCl salt) 162–164 (MeOH/Et_2O)	3402, 2945, 2736, 2558, 1643, 1584, 1460, 1384, 1290, 1112, 1072, 954, 754, 702	1.08–1.24(3H, m), 1.58–2.02(4H, m), 2.06–2.23(2H, m), 2.12 & 2.14(6H, each s), 2.29(6H, s), 2.53–2.67(2H, m), 2.78(2H, m), 3.07(2H, m), 3.20 & 3.38(2H, each q), 3.27–3.57 & 4.49(3H, m), 3.61(2H, s), 7.15–7.34(5H, m)
77		pale yellow cryst. (HCl salt) 177–179 (MeOH/Et_2O)	3410, 2937, 2592, 1642, 1485, 1460, 1431, 1377, 1323, 1285, 1215, 1132, 1112, 1028, 976, 946	1.05–1.16(3H, m), 1.33–2.26(6H, m), 1.52 & 1.55(3H, each d), 2.09(3H, s), 2.11 & 2.12(3H, s), 2.18(3H, s), 2.90–3.53 (6H, m), 3.11 & 3.15(2H, each d), 4.11 & 4.42(1H, m), 4.72 & 4.79(1H, each q), 6.25(1H, m), 6.43–6.62(2H, m), 7.23(1H, t), 7.27–7.40(4H, m)

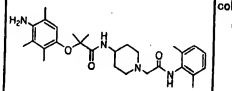
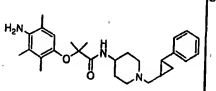
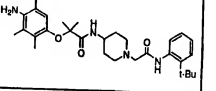
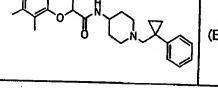
No.	Chemical Structure	Properties m. p. (℃) (solvent)	IR (KBr): cm^{-1} (HCl salt)	^{1}H-NMR ($CDCl_3$)
78		colorless cryst. (HCl salt) 185-187 (MeOH/Et_2O)	3406, 2939, 2710, 2555, 1646, 1580, 1450, 1384, 1278, 1211, 1113, 1072, 980, 946	1.16(3H, m), 1.45-2.20(6H, m), 2.12 & 2.14(6H, each s), 2.28(6H, s), 3.05(2H, m), 3.10-3.23(2H, m), 3.27-3.63 & 4.50(4H, m), 3.37 & 3.48(2H, each q), 3.61(2H, s), 6.16-6.33(1H, m), 6.50 & 6.52(1H, each d), 7.22(1H, t), 7.31(2H, t), 7.37(2H, d)
79		colorless cryst. (HCl salt)	3442, 2941, 1684, 1618, 1534, 1489, 1399, 1156, 1081	1.56(6H, s), 1.40-1.75(2H, m), 1.75-1.95(2H, m), 2.06, 2.08, 2.09, 2.10, 2.14 & 2.16(9H, each s), 2.28 & 2.49 (2H, m), 2.86 & 2.88(2H, each s), 2.95 & 3.15(3H, s), 2.95-3.15(2H, m), 3.20-3.45(2H, m), 3.85-4.10(2H, m), 4.61 & 4.76(1H, m), 6.32 & 6.37(1H, s), 6.79(1H, s), 8.35 & 8.36(1H, s), 9.59 & 9.64(1H, s)
80		colorless cryst. (HCl salt)	3418, 2936, 2587, 1654, 1522, 1480, 1312, 1156, 1094, 945, 749, 695	1.42(6H, s), 1.45-1.70(2H, m), 1.95-2.10(2H, m), 2.09(3H, s), 2.11(3H, s), 2.14(3H, s), 2.15-2.30(2H, m), 2.85-2.95(2H, m), 3.15(2H, d), 3.42(2H, brs), 3.87(1H, m), 6.26(1H, dt), 6.51(1H, d), 6.56(1H, s), 6.91(1H, d), 7.22(1H, t), 7.30(2H, t), 7.37(2H, d)
81		pale yellow cryst. (HCl salt) 205-208 (MeOH/Et_2O)	3418, 2932, 2580, 1668, 1532, 1482, 1157, 1107, 701	0.70-0.73(2H, m), 0.84-0.88(2H, m), 1.41(6H, s), 1.35-1.50(2H, m), 1.80-1.90(2H, m), 2.10(3H, s), 2.11(3H, s), 2.14(3H, s), 2.04-2.20(2H, m), 2.55(2H, s), 2.75-2.95(2H, m), 3.41(2H, brs), 3.79(1H, m), 6.54(1H, s), 6.83(1H, d), 7.16(1H, t), 7.25(2H, t), 7.32(2H, d)

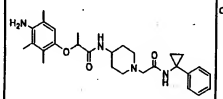
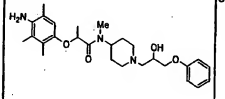
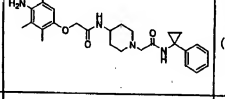
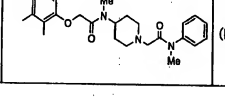
No.	Chemical Structure	Properties m. p. (°C) (solvent)	IR (KBr) : cm^{-1} (HCl salt)	^{1}H-NMR ($CDCl_3$)
82		colorless cryst. (HCl salt)	3360, 2968, 2807, 1687, 1654, 1560, 1534, 1500, 1448, 1346, 1157, 1098, 950, 762, 692	1.44(6H, s), 1.45-1.70(2H, m), 2.00-2.25(2H, m), 2.11(3H, s), 2.12(3H, s), 2.17(3H, s), 2.40-2.55(2H, m), 2.80-3.05(2H, m), 3.13(2H, s), 3.35-3.55(2H, bre), 3.85-4.00(1H, m), 6.55(1H, s), 6.92(1H, d), 7.10 (1H, t), 7.33(2H, t), 7.55(2H, d)
83		colorless cryst. (HCl salt) 188-190 (EtOH/Et_2O)	3424, 2938, 2495, 1884, 1601, 1556, 1500, 1448, 1316, 1148, 1116	1.45-1.83(2H, m), 1.51(3H, d), 2.00(2H, m), 2.13(3H, s), 2.14(3H, s), 2.21(3H, s), 2.44(2H, m), 2.83(2H, m), 3.11(2H, s), 3.41(2H, bre), 3.90(1H, m), 4.45(1H, q), 6.48(1H, s), 6.57 & 6.59(1H, bre), 7.10 (1H, t), 7.33(2H, t), 7.55(2H, d), 9.04(1H, bre)
84		pale yellow cryst. (HCl salt) 232-235 (EtOH/Et_2O)	3424, 3193, 2938, 2806, 2594, 1680, 1590, 1552, 1486, 1153, 1118	1.41-1.51(2H, m), 1.50(3H, d), 1.94(2H, m), 2.06-2.23(2H, m), 2.11(3H, s), 2.13(3H, s), 2.18(3H, s), 2.85(2H, m), 3.13(2H, d), 3.38(2H, bre), 3.86(1H, m), 4.44(1H, q), 6.24(1H, dt), 6.48(1H, s), 6.50(1H, d), 6.54(1H, bre), 7.20-7.23(1H, m), 7.30(2H, t), 7.35-7.37 (2H, m)
85		colorless cryst. (HCl salt) 178-181 (MeOH/Et_2O)	3402, 3247, 2946, 2592, 1668, 1600, 1556, 1491, 1448, 1315, 1128, 949	1.48-1.66(2H, m), 2.00-2.09(2H, m), 2.13(3H, s), 2.16(3H, s), 2.21(3H, s), 2.38-2.57(2H, m), 2.86(2H, m), 3.13(2H, s), 3.41(2H, bre), 3.97(1H, m), 4.38(2H, s), 6.50(1H, s), 6.60(1H, bre), 7.11(1H, t), 7.33(2H, m), 7.58(2H, d), 9.04(1H, bre)

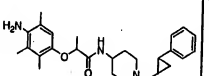
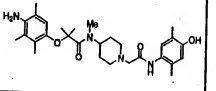
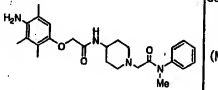
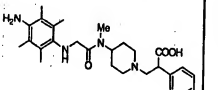
No.	Chemical Structure	Properties m. p. (℃) (solvent)	IR (KBr): cm^{-1} (HCl salt)	^{1}H-NMR ($CDCl_3$)
86		pale yellow cryst. (HCl salt) 196-198 (MeOH/Et_2O)	3326, 2934, 2518, 1662, 1547, 1486, 1451, 1326, 1285, 1238, 1214, 1130, 976, 942	1.46-1.75(2H, m), 1.94-2.03(2H, m), 2.09-2.25(2H, m), 2.11(3H, s), 2.15(3H, s), 2.17(3H, s), 2.78-2.99 (2H, m), 3.15(2H, d), 3.39(2H, brs), 3.93(1H, m), 4.36(2H, s), 6.26(1H, dt), 6.47-6.63(2H, m), 6.49 (1H, s), 7.22(1H, t), 7.30(2H, m), 7.37(2H, d)
87		colorless cryst. (HCl salt) 184-187 (MeOH/Et_2O)	3404, 2936, 2579, 1642, 1485, 1461, 1432, 1376, 1322, 1286, 1245, 1215, 1112, 1027	0.64-0.74 & 0.81-0.90(4H, m), 1.06(3H, m), 1.19-1.28(1H, m), 1.44-1.77(2H, m), 1.50 & 1.52(3H, each d), 1.82-1.91(2H, m), 1.97-2.23(1H, m), 2.08 & 2.09(3H, each s), 2.10 & 2.11(3H, each s), 2.16(3H, s), 2.51 & 2.55(2H, each s), 2.87-3.05(2H, m), 3.09-3.55(4H, m), 3.98 & 4.29(1H, m), 4.69 & 4.76(1H, each q), 6.48 & 6.50(1H, each s), 7.13-7.20(1H, m), 7.22-7.38(4H, m)
88		colorless cryst. (HCl^1 salt) 183-186 (MeOH/Et_2O)	3403, 2944, 2728, 2563, 1646, 1581, 1460, 1432, 1296, 1113, 1069, 1028, 943	0.66-0.76 & 0.82-0.88(4H, m), 1.06-1.16(3H, m), 1.44-1.76, 1.81-1.92 & 1.97-2.30(6H, m), 2.12 & 2.14(6H, each s), 2.24 & 2.27(6H, each s), 2.52 & 2.56(2H, each s), 2.96-3.05(2H, m), 3.11 & 3.30(2H, each q), 3.24 & 4.37(1H, m), 3.34-3.65(2H, brs), 3.57(2H, s), 7.13-7.22(1H, m), 7.23-7.36(4H, m)
89		colorless cryst. (HCl salt) 183-186 (MeOH/Et_2O)	3402, 2944, 2591, 1692, 1640, 1530, 1486, 1385, 1302, 1285, 1132, 1100	1.65-1.77(2H, m), 1.78-1.90(1H, m), 1.90-2.03(1H, m), 2.10 (3H, s), 2.16 & 2.20(6H, each s), 2.33-2.55(2H, m), 2.88 & 2.95(3H, each s), 2.92-3.03(2H, m), 3.15 & 3.18(2H, each s), 3.36(2H, brs), 3.94 & 4.51(1H, m), 3.99(2H, brs), 4.58 & 4.61 (2H, each s), 6.55 & 6.59(1H, each s), 6.81(1H, s), 8.36 & 8.37(1H, each s), 9.56 & 9.64(1H, brs)

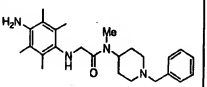
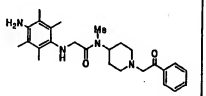
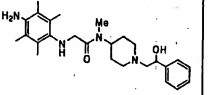
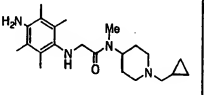
No.	Chemical Structure	Properties m. p. (°C) (solvent)	IR (KBr): cm^{-1} (HCl salt)	^{1}H-NMR ($CDCl_3$)
90		colorless cryst. (HCl salt) 172–175 (iso-PrOH/ Et_2O)	3416, 2939, 2600, 1634, 1486, 1416, 1323, 1112, 1028, 763, 704	0.68–0.72 & 0.83–0.86(4H, m), 1.24–1.26 & 1.39–1.42 (2H, m), 1.51 & 1.53(3H, each d), 1.56–1.77(2H, m), 1.89 & 2.04(2H, m), 2.09(3H, s), 2.11 & 2.12(3H, each s), 2.15(3H, s), 2.52 & 2.55(2H, each s), 2.76 & 2.84(3H, each s), 2.97(2H, m), 3.31(2H, brs), 4.00 & 4.38(1H, m), 4.76 & 4.79(1H, each q), 6.43 & 6.49(1H, each s), 7.14–7.21(1H, m), 7.23–7.32(4H, m)
91		colorless cryst. (HCl salt) 221–224 (MeOH/Et_2O)	3258, 1657, 1601, 1556, 1500, 1448, 1408, 1315, 1106, 953, 756, 694	1.69(2H, m), 2.09(3H, s), 2.09–2.10(2H, m), 2.22(3H, s), 2.25(3H, s), 2.49(2H, m), 2.91(2H, m), 3.15(2H, s), 3.59(2H, brs), 4.01(1H, m), 4.27(2H, s), 7.00(1H, brs), 7.11(1H, t), 7.34(2H, t), 7.57(2H, d), 9.09(1H, brs)
92		pale brown cryst. (HCl salt) 213–219 (EtOH/Et_2O)	3424, 2948, 1692, 1634, 1534, 1497, 1456, 1398, 1319, 1304, 1101, 1049, 950	1.73–1.84(4H, m), 2.08(3H, s), 2.25(6H, s), 2.49(2H, m), 2.92 & 3.03(3H, each s), 2.99–3.03(2H, m), 3.16(2H, s), 3.55(2H, brs), 3.99(2H, brs), 4.27 & 4.55(1H, m), 4.47 (2H, s), 6.81(1H, s), 8.38(1H, s), 9.63 & 9.66(1H, brs)
93		colorless cryst. (HCl salt) 193–197 (MeOH/Et_2O)	3208, 2972, 1632, 1549, 1520, 1463, 1412, 1320, 1104, 952	1.24(3H, m), 1.85–2.03(4H, m), 2.07(3H, s), 2.21(6H, s), 2.25(3H, s), 2.26(3H, s), 2.45(2H, m), 3.03(2H, m), 3.16(2H, s), 3.39 & 3.44(2H, m), 3.56(2H, brs), 4.25 (1H, m), 4.46(2H, s), 4.70(1H, s), 6.62(1H, s), 7.61 (1H, s), 8.88 & 8.95(1H, brs)

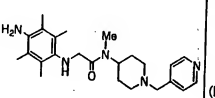
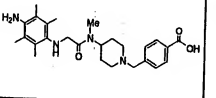
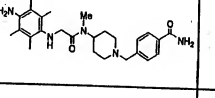
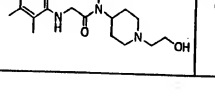
No.	Chemical Structure	Properties m. p. (℃) (solvent)	IR (KBr) : cm^{-1} (HCl salt)	^{1}H-NMR ($CDCl_3$)
94		colorless cryst. (HCl salt) 178-181 (MeOH/Et_2O)	3402, 2944, 2726, 2554, 1643, 1464, 1426, 1391, 1290, 1073	0.77-0.86, 0.92-1.01 & 1.10-1.28(3H, m), 1.14 & 1.16(3H, each t), 1.42-2.02(5H, m), 2.04-2.42(3H, m), 2.12 & 2.14 (6H, each s), 2.24 & 2.28(6H, each s), 2.50 & 2.53(1H, each dd), 3.04-3.16(2H, m), 3.18 & 3.36(2H, each q), 3.23-3.52 (2H, brs), 3.29 & 4.46(1H, m), 3.60(2H, s), 7.01-7.07(2H, m), 7.14(1H, t), 7.20-7.29(2H, m)
95		colorless cryst. (HCl salt) 178-180 (MeOH:Et_2O)	3416, 2943, 1672, 1544, 1486, 1460, 1390, 1326, 1284, 1240, 1215, 1128, 951	0.77-0.86, 0.92-1.00 & 1.16-1.28(3H, m), 1.49-1.63 (2H, m), 1.67(1H, m), 1.92-2.02(2H, m), 2.11(3H, s), 2.15(3H, s), 2.17(3H, s), 2.09-2.27(2H, m), 2.36(1H, dd), 2.50(1H, dd), 2.92(2H, m), 3.38(2H, brs), 3.91(1H, m), 4.36(2H, s), 6.48(1H, s), 6.58(1H, brs), 7.04(2H, d), 7.14(1H, t), 7.18-7.27(2H, m)
96		colorless cryst. (HCl salt) 175-178 (MeOH/Et_2O)	3402, 2944, 2592, 1672, 1590, 1545, 1487, 1460, 1325, 1286, 1241, 1132, 1027	0.71(2H, m), 0.85(2H, m), 1.41(2H, m), 1.75-1.90(2H, m), 2.07-2.22(2H, m), 2.11(3H, s), 2.14(3H, s), 2.16 (3H, s), 2.55(2H, s), 2.82(2H, m), 3.38(2H, brs), 3.84 (1H, m), 4.33(2H, s), 6.47(1H, s), 6.50(1H, brs), 7.16 (1H, t), 7.22-7.28(2H, m), 7.29-7.34(2H, m)
97		colorless cryst. (HCl salt) 208-211 (MeOH/Et_2O)	2944, 2508, 1663, 1588, 1545, 1487, 1456, 1314, 1282, 1239, 1214, 1129	1.46-1.63(2H, m), 1.94-2.03(2H, m), 2.12(3H, s), 2.15(3H, s), 2.18(3H, s), 2.23(2H, m), 2.59(2H, m), 2.79(2H, m), 2.89(2H, m), 3.39(2H, brs), 3.93(1H, m), 4.37(2H, s), 6.49(1H, s), 6.58(1H, brs), 7.16-7.22(3H, m), 7.24-7.34(2H, m)

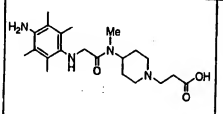
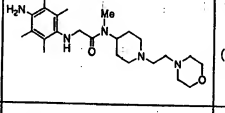
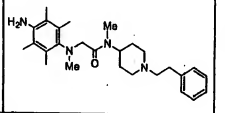
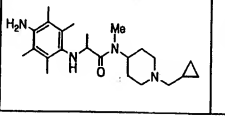
No.	Chemical Structure	Properties m. p. (℃) (solvent)	IR (KBr): cm^{-1} (HCl salt)	^1H-NMR ($CDCl_3$)
98		colorless cryst. (HCl salt)	3417, 2932, 1672, 1534, 1477, 1157, 1095, 953, 774	1.43(6H, s), 1.45-1.70(2H, m), 2.03-2.20(2H, m), 2.10(3H, s), 2.12(3H, s), 2.15(3H, s), 2.22(6H, s), 2.53(2H, m), 2.90-3.05(2H, m), 3.20(2H, s), 3.42(2H, brs), 3.93(1H, m), 6.55(1H, s), 6.92(1H, d), 7.08(3H, m), 8.61(1H, brs)
99		colorless cryst. (HCl salt)	3416, 2934, 2586, 1654, 1522, 1477, 1155, 1094, 700	0.78-0.85(1H, m), 0.93-0.98(1H, m), 1.18-1.28(1H, m), 1.41 (3H, s), 1.42(3H, s), 1.45-1.63(2H, m), 1.67(1H, m), 1.92-2.02(2H, m), 2.09(3H, s), 2.10(3H, s), 2.14(3H, s), 2.15-2.28(2H, m), 2.37(1H, dd), 2.50(1H, dd), 2.85-3.05(2H, m), 3.35-3.50(2H, brs), 3.84(1H, m), 6.56(1H, s), 6.89 (1H, d), 7.04(2H, d), 7.13(1H, t), 7.20-7.31(2H, m)
100		colorless cryst. (HCl salt)	3424, 2968, 1676, 1534, 1482, 1157, 1091, 953, 764	1.43 & 1.44(15H, each s), 1.45-1.65(2H, m), 1.95-2.10(2H, m), 2.10 & 2.12(6H, s), 2.16(3H, s), 2.45-2.65(2H, m), 2.85-3.00(2H, m), 3.19(2H, s), 3.35-3.50(2H, brs), 3.85-4.00(1H, m), 6.56(1H, s), 6.93(1H, d), 7.11(1H, t), 7.20-7.30(1H, m), 7.38(1H, d), 7.95(1H, d), 9.36(1H, brs)
101		colorless cryst. (HCl salt) 200-203 ($EtOH/Et_2O$)	3419, 2942, 2580, 1691, 1666, 1592, 1487, 1459, 1428, 1152, 1118, 1040, 760, 701	0.70, 0.84 & 1.35(6H, m), 1.47(3H, d), 1.80(2H, m), 2.05-2.16(2H, m), 2.10(3H, s), 2.12(3H, s), 2.16(3H, s), 2.52(2H, s), 2.75-2.83(2H, m), 3.37(2H, brs), 3.76 (1H, m), 4.40(1H, q), 6.45(1H, s), 6.45-6.47(1H, brs), 7.17(1H, t), 7.22-7.26(2H, m), 7.30-7.32(2H, m)

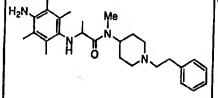
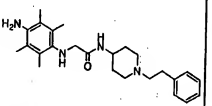
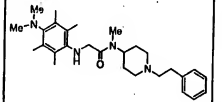
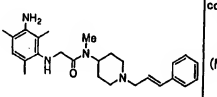
No.	Chemical Structure	Properties m. p. (°C) (solvent)	IR (KBr): cm^{-1} (HCl salt)	^1H-NMR ($CDCl_3$)
102		colorless cryst. (HCl salt) 190-194 ($EtOH/Et_2O$)	3418, 1684, 1541, 1498, 1486, 1460, 1324, 1149, 1116, 1030, 956	1.21-1.30(4H, m), 1.41-1.55(2H, m), 1.50(3H, d), 1.94(2H, m), 2.12(3H, s), 2.14(3H, s), 2.19(3H, s), 2.33(2H, m), 2.65-2.73(2H, m), 2.97(2H, s), 3.40(2H, brs), 3.85(1H, m), 4.43(1H, q), 6.46(1H, s), 6.53 (1H, brs), 7.18-7.31(5H, m), 7.67(1H, brs)
103		colorless cryst. (HCl salt) 143-147 (iso-PrOH/ Et_2O)	2938, 1634, 1599, 1492, 1417, 1114, 1040, 759, 694	1.54(3H, d), 1.56-1.88(4H, m), 2.10(3H, s), 2.13 & 2.14 (3H, each s), 2.17(3H, s), 2.24(2H, m), 2.53(2H, m), 2.83 & 2.92(3H, each s), 3.06(2H, m), 3.34(2H, brs), 3.97(2H, d), 4.03-4.06(1H, m), 4.15 & 4.47-4.53(1H, m), 4.77-4.85 (1H, m), 6.45 & 6.51(1H, each s), 6.91-6.97(3H, m), 7.26-7.31(2H, m)
104		colorless cryst. (HCl salt) 180-183 ($MeOH/Et_2O$)	3402, 3217, 2945, 1680, 1540, 1487, 1458, 1324, 1283, 1127, 1030, 956	1.25, 1.28, 1.46-1.64 & 1.93-2.03(8H, m), 2.12(3H, s), 2.15(3H, s), 2.19(3H, s), 2.36(2H, m), 2.73(2H, m), 2.99(2H, s), 3.40(2H, brs), 3.92(1H, m), 4.36(2H, s), 6.49(1H, s), 6.57(1H, brs), 7.14-7.22(1H, m), 7.23-7.32(4H, m), 7.69(1H, brs)
105		colorless cryst. (HCl salt) 178-180 ($MeOH/Et_2O$)	3417, 2944, 2592, 1664, 1595, 1496, 1418, 1371, 1321, 1285, 1142, 1129, 1103, 1033	1.46-1.62(2H, m), 1.70-1.95(2H, m), 2.01-2.22(2H, m), 2.09(3H, s), 2.14(3H, s), 2.18(3H, s), 2.76-3.01(2H, m), 2.83 & 2.90(3H, each s), 2.92(2H, s), 3.27(3H, s), 3.33 (2H, brs), 3.74 & 4.39(1H, m), 4.54 & 4.56(2H, each s), 6.52 & 6.56(1H, each s), 7.19(2H, t), 7.29-7.37(1H, m), 7.41(2H, t)

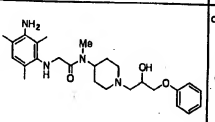
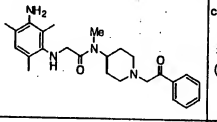
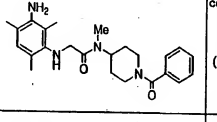
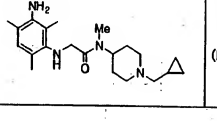
No.	Chemical Structure	Properties m. p. (°C) (solvent)	IR (KBr) : cm^{-1} (HCl salt)	^{1}H-NMR ($CDCl_3$)
106		colorless cryst. (HCl salt) 173-176 (iso-PrOH/ Et_2O)	3423, 1664, 1605, 1544, 1485, 1462, 1386, 1324, 1116, 1034, 953	0.81, 0.95 & 1.20(3H, m), 1.50(3H, d), 1.58(2H, m), 1.66(1H, m), 1.92(2H, m), 2.11(3H, s), 2.12 & 2.13(3H, s), 2.17(3H, s), 2.19(2H, m), 2.33-2.37(1H, m), 2.46-2.51 (1H, m), 2.90(2H, m), 3.38(2H, brs), 3.83(1H, m), 4.44 (1H, q), 6.47(1H, s), 6.52(1H, m), 7.03(2H, d), 7.13 (1H, t), 7.21-7.26(2H, m)
107		colorless cryst. (HCl salt)	3426, 2943, 1684, 1619, 1552, 1518, 1466, 1411, 1157, 1089, 872	1.40-1.88(4H, m), 1.56 & 1.57(6H, each s), 2.00-2.32(1H, m), 2.07, 2.08, 2.10, 2.15 & 2.17(15H, each s), 2.47(1H, t), 2.86 & 3.14(3H, each s), 2.85-3.10(2H, m), 3.10 & 3.16(2H, each s), 3.34(2H, brs), 4.57 & 4.77(1H, m), 5.35(1H, brs), 6.32 & 6.37(1H, each s), 6.55(1H, s), 7.48 & 7.50(1H, each s), 8.85(1H, brs)
108		colorless cryst. (HCl salt) 176-178 (MeOH/Et_2O)	3417, 2934, 1668, 1595, 1544, 1496, 1454, 1372, 1285, 1240, 1129, 981	1.45-1.65(2H, m), 1.84-1.93(2H, m), 2.08-2.23(2H, m), 2.11(3H, s), 2.15(3H, s), 2.16(3H, s), 2.77(2H, m), 2.92(2H, s), 3.27(3H, s), 3.39(2H, brs), 3.85(1H, m), 4.34(2H, s), 6.48(1H, s), 6.53(1H, brs), 7.19(2H, d), 7.30-7.37(1H, m), 7.41(2H, m)
109		foamy substance (HCl salt)	2565, 1720, 1650, 1498, 1456, 1422, 1396, 1201, 1007, 949, 799	HCl salt in DMSO-d_6 & $CDCl_3$: 1.78(2H, m), 2.08-2.44(2H, m), 2.14(6H, s), 2.28(6H, s), 2.77-3.04(2H, m), 2.81 & 2.90 (3H, each s), 3.25(1H, dd), 3.44-3.69(2H, m), 3.77-3.90 (1H, m), 3.82(2H, s), 4.26(1H, dd), 4.72(1H, m), 7.32 (5H, m)

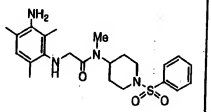
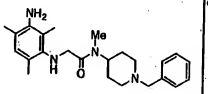
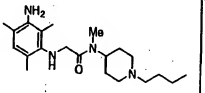
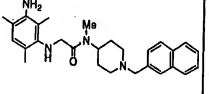
No.	Chemical Structure	Properties m. p. (℃) (solvent)	IR (KBr) : cm^{-1} (HCl salt)	^{1}H-NMR (DMSO-d_6): HCl salt
110		white amorphous (HCl salt)	1646, 1497, 1456, 1418, 1309, 1118, 1005, 945, 752, 704	1.67 & 1.78(2H, d), 2.10-2.50(16H, m), 2.77 & 2.80 (3H, each s), 2.96(1H, m), 3.06(1H, m), 3.34(2H, m), 3.79 & 4.57(1H, m), 3.98 & 4.13(2H, each s), 4.26(2H, m), 7.45(3H, m), 7.65(2H, m), 11.4 & 11.5(1H, s)
111		pale yellow powder (HCl salt) 218-220 (EtOH/Et_2O)	3426, 2940, 1692, 1651, 1597, 1450, 1392, 1307, 1263, 1233, 1153, 1109	1.75 & 1.83(2H, m), 2.20(6H, s), 2.24(6H, s), 2.20-2.32 (2H, m), 2.81 & 2.84(3H, each s), 3.27-3.43(2H, m), 3.60(2H, m), 3.93 & 4.51(2H, m), 4.60(1H, m), 5.03 & 5.07(2H, each s), 7.63(2H, m), 8.00(2H, m)
112		white cryst. (HCl salt) 188-190 (MeOH/Et_2O)	3418, 2947, 1650, 1500, 1454, 1415, 1312, 1201, 1153, 1106, 1069, 1029	1.71 & 1.83(2H, m), 2.18(6H, s), 2.22(6H, s), 2.18-2.23 (2H, m), 2.79 & 2.81(3H, each s), 3.09-3.19(4H, m), 3.72(2H, m), 3.90 & 4.08(2H, each s), 4.59(1H, m), 5.18(1H, m), 7.32-7.43(5H, m)
113		white amorphous (HCl salt)	3418, 2948, 1647, 1458, 1420, 1311, 1280, 1202, 1100, 1064, 1031, 950	0.40(2H, m), 0.63(2H, m), 1.11(1H, m), 1.69 & 1.81(2H, d), 2.10-2.40(4H, m), 2.79 & 2.81(3H, each s), 3.15-3.80 (4H, m), 3.55(2H, t), 3.82 & 4.58(1H, m), 3.94 & 4.10 (2H, each s), 10.87(1H, brs)

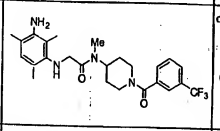
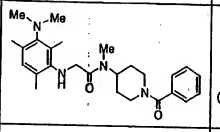
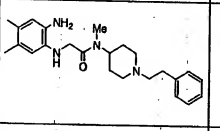
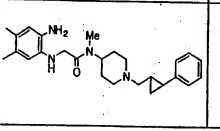
No.	Chemical Structure	Properties m. p. (°C) (solvent)	IR (KBr) : cm^{-1} (HCl salt)	^{1}H-NMR (DMSO-d_6): HCl salt
114		pale yellow cryst. (HCl salt) >250 (MeOH/EtOH)	3448, 1638, 1603, 1508, 1373, 1308, 1263, 1193, 1110, 1070, 1008, 949, 798	1.67 & 1.80(2H, d), 2.19 & 2.22(12H, s), 2.30-2.50(2H, m), 2.77 & 2.80(3H, each s), 2.90-3.30(2H, m), 3.42(2H, d), 3.82 & 4.59(1H, m), 3.92 & 4.08(2H, each s), 4.47 & 4.50(2H, each s), 11.95(1H, brs)
115		pale yellow amorphous (HCl salt)	1708, 1654, 1418, 1272, 1182, 1108, 1067, 1020, 1005, 944, 871, 755	1.67 & 1.78(2H, d), 2.10-2.40(14H, m), 2.77 & 2.80(3H, each s), 2.90-3.10(1H, m), 3.10-3.30(1H, m), 3.30-3.50 (2H, m), 3.77 & 4.57(1H, m), 3.97 & 4.12(2H, each s), 4.30-4.60(2H, m), 7.77(2H, t), 7.90-8.10(2H, m), 11.42 & 11.52(1H, brs)
116		pale yellow solid (HCl salt)	3412, 2937, 1652, 1568, 1422, 1394, 1308, 1118, 1104, 943, 869	free base in $CDCl_3$: 1.50-2.20(6H, m), 2.12(6H, s), 2.27 (6H, s), 2.75 & 2.90(3H, each s), 2.85-2.95(2H, m), 3.32 & 4.54(1H, m), 3.53(2H, d), 3.59(2H, d), 7.40(2H, t), 7.76(2H, d)
117		white amorphous (HCl salt)	3397, 2951, 2748, 1648, 1584, 1460, 1422, 1310, 1155, 1080, 980	1.68 & 1.80(2H, d), 2.00-2.40(12H, m), 2.77 & 2.80 (3H, each s), 3.00-3.50(4H, m), 3.55(2H, t), 3.78(2H, q), 3.83 & 4.59(1H, m), 3.95 & 4.12(2H, each s), 10.47(1H, brs)

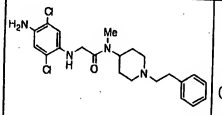
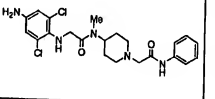
No.	Chemical Structure	Properties m. p. (°C) (solvent)	IR (KBr) : cm^{-1} (HCl salt)	^{1}H-NMR (DMSO-d_6): HCl salt
118		pale yellow amorphous (HCl salt)	1730, 1659, 1643, 1581, 1496, 1424, 1378, 1312, 1221, 1071, 1035, 950, 866, 801	1.68 & 1.80(2H, d), 2.00-2.04(14H, m), 2.78 & 2.80 (3H, each s), 2.85(2H, m), 2.98 & 3.17(2H, m), 3.23(2H, brs), 3.48(2H, brs), 3.83 & 4.58(1H, m), 4.03 & 4.20 (2H, each s), 11.12(1H, brs)
119		colorless cryst. (HCl salt) >240 : (MeOH/Et_2O)	1646, 1629, 1496, 1456, 1361, 1308, 1277, 1092, 980, 917	1.75 & 1.87(2H, d), 2.10-2.40(14H, m), 2.77 & 2.79 (3H, each s), 3.40-4.10(12H, m), 4.62(1H, m), 11.01 & 11.36(2H, s)
120		white amorphous (HCl salt)	3424, 2940, 1652, 1456, 1366, 1298, 1245, 1160, 1105, 1066	1.63-1.73(2H, m), 2.11-2.33(2H, m), 2.21(6H, s), 2.24 (6H, s), 2.70 & 2.72(3H, each s), 2.76 &2.79(3H, each s), 2.96-3.09(4H, m), 3.23(2H, m), 3.57(2H, m), 3.80(2H, s), 4.55(1H, m), 7.24-7.29(3H, m), 7.33-7.37(2H, m)
121		white amorphous (HCl salt)	2942, 2710, 1656, 1642, 1462, 1453, 1416, 1311, 1250, 1075, 1033, 948	free base in $CDCl_3$: 0.09(2H, m), 0.51(2H, m), 0.85(1H, m), 1.20 & 1.27(3H, each d), 1.42-2.30(8H, m), 2.09(3H, s), 2.10(3H, s), 2.23(3H, s), 2.25(3H, s), 2.69 & 2.77(3H, each s), 2.96 & 3.11(2H, m), 3.19 & 4.48(1H, m), 3.40(2H, brs), 3.94(1H, m)

No.	Chemical Structure	Properties m. p. (℃) (solvent)	IR (KBr): cm^{-1} (HCl salt)	^{1}H-NMR ($CDCl_3$)
122		colorless cryst. (HCl salt) 205-209 (MeOH/Et_2O)	2937, 2690, 1646, 1493, 1456, 1314, 1247, 1072, 1031, 1015	1.21 & 1.28(3H, each d), 1.45-1.98(4H, m), 2.05-2.23 (2H, m), 2.09(3H, s), 2.11(3H, s), 2.23(3H, s), 2.25(3H, s), 2.50-2.65(2H, m), 2.70 & 2.78(3H, each s), 2.72-2.92 (2H, m), 3.05(2H, m), 3.24 & 4.50(1H, m), 3.40(2H, brs), 3.94(1H, m), 7.13-7.36(5H, m)
123		white amorphous (HCl salt)	3376, 2936, 2714, 1675, 1560, 1456, 1316, 1282, 1252, 1142, 1115, 1067, 956	1.48-1.64(2H, m), 1.97-2.06(2H, m), 2.11(6H, s), 2.19-2.29(2H, m), 2.23(6H, s), 2.57-2.65(2H, m), 2.76-2.90 (2H, m), 2.93(2H, m), 3.45(2H, s), 3.49(2H, brs), 3.92 (1H, m), 7.17-7.33(5H, m)
124		white amorphous (HCl salt)	3443, 2959, 2716, 1652, 1456, 1364, 1313, 1283, 1162, 1018, 758, 705	1.60-2.10(4H, m), 2.10-2.30(2H, m), 2.19(6H, s), 2.24(6H, s), 2.50-2.70(2H, m), 2.70-2.80(2H, m), 2.76 & 2.80 & 2.90(9H, each s), 3.06 & 3.09(2H, d), 3.32 & 4.55(1H, m), 3.68 & 3.71(2H, each s)
125		colorless cryst. (HCl salt) 174-176 (MeOH/Et_2O)	2937, 2717, 1646, 1577, 1489, 1451, 1334, 1306, 1284, 1153, 1109, 1029, 978, 944	1.42-2.06(6H, m), 2.12(3H, s), 2.18(3H, s), 2.25(3H, s), 2.77 & 2.90(3H, each s), 2.98-3.62(6H, m), 3.32 & 4.58 (1H, m), 3.69 & 3.72(2H, each s), 6.20-6.38(1H, m), 6.53(1H, m), 6.74 & 6.75(1H, each s), 7.20-7.28(1H, m), 7.32(2H, m), 7.35-7.42(2H, m)

No.	Chemical Structure	Properties m. p. (℃) (solvent)	IR (KBr): cm^{-1} (HCl salt)	^1H-NMR ($CDCl_3$)
126		colorless cryst. (HCl salt) 163-165 ($MeOH/Et_2O$)	2946, 2751, 1650, 1599, 1491, 1242, 1154, 1110, 1079, 1042, 947, 762	1.47-2.35(6H, m), 2.12(3H, s), 2.19(3H, s), 2.24 & 2.25 (3H, each s), 2.28-2.44(2H, m), 2.77 & 2.90(3H, each s), 2.94-3.20(2H, m), 3.33 & 4.57(1H, m), 3.49(2H, brs), 3.70 & 3.73(2H, each s), 3.98(2H, d), 4.03-4.18(1H, m), 6.74 & 6.76(1H, each s), 6.89-7.00(3H, m), 7.24-7.33 (2H, m)
127		colorless cryst. (HCl salt) 182-188 ($MeOH/Et_2O$)	3425, 2935, 2562, 1693, 1648, 1597, 1488, 1451, 1394, 1306, 1262, 1232, 1107, 1078, 952, 759	1.38-2.35(6H, m), 2.12(3H, s), 2.19(3H, s), 2.24 & 2.25 (3H, each s), 2.77 & 2.90(3H, each s), 3.03-3.15(2H, m), 3.34 & 4.57(1H, m), 3.38-3.62(2H, brs), 3.70 & 3.73(2H, each s), 3.84 & 3.85(2H, each s), 6.74 & 6.76(1H, each s), 7.47(2H, m), 7.58(1H, m), 7.98(2H, m)
128		colorless cryst. (HCl salt) 166-168 ($MeOH/Et_2O$)	2936, 2573, 1646, 1618, 1575, 1469, 1448, 1324, 1279, 1130, 1022, 788	1.45-1.83(4H, m), 2.12(3H, s), 2.17 & 2.18(3H, each s), 2.23 & 2.25(3H, each s), 2.76 & 2.89(3H, each s), 3.14 (1H, m), 3.49(2H, brs), 3.56 & 4.78(1H, m), 3.71 & 3.75 (2H, each s), 3.89(1H, m), 4.49(1H, m), 4.85(1H, m), 6.74(1H, s), 7.41(5H, m)
129		colorless cryst. (HCl salt) 173-175 ($MeOH/Et_2O$)	3424, 2593, 1638, 1573, 1490, 1404, 1360, 1312, 1281, 1201, 1107, 1031, 948	0.02-0.17(2H, m), 0.45-0.56(2H, m), 0.85(1H, m), 1.46-1.82 (4H, m), 1.84-2.31(4H, m), 2.12(3H, s), 2.19(3H, s), 2.25 & 2.26(3H, each s), 2.76 & 2.90(3H, each s), 3.07-3.21 (2H, m), 3.29 & 4.51(1H, m), 3.49(2H, brs), 3.69 & 3.72 (2H, each s), 4.37-4.61(1H, m), 6.74 & 6.75(1H, each s)

No.	Chemical Structure	Properties m. p. (℃) (solvent)	IR (KBr): cm^{-1} (HCl salt)	^{1}H-NMR ($CDCl_3$)
130		white amorphous (HCl salt)	2933, 2852, 1656, 1648, 1584, 1486, 1447, 1333, 1307, 1187, 1094, 1024, 936, 740	1.46-1.70(2H, m), 1.72-1.85(2H, m), 2.11(3H, s), 2.15(3H, s), 2.21(3H, s), 2.72 & 2.84(3H, each s), 3.38-3.54(2.5H, m), 3.59 & 3.67(2H, each s), 3.91(2H, m), 4.42(1.5H, m), 6.71 & 6.72(1H, each s), 7.55(2H, t), 7.63(1H, t), 7.70(2H, d)
131		colorless cryst. (HCl salt) 176-178 (MeOH/Et_2O)	2937, 2727, 1648, 1489, 1455, 1420, 1309, 1105, 1031, 946	1.48-2.28(6H, m), 2.11(3H, s), 2.18(3H, s), 2.23 & 2.24 (3H, each s), 2.75 & 2.89(3H, each s), 2.94(2H, m), 3.29 & 4.38-4.60(2H, m), 3.50(4H, m), 3.68 & 3.71(2H, each s), 6.73 &6.75(1H, each s), 7.20-7.35(5H, m)
132		colorless cryst. (HCl salt) 172-174 (MeOH/Et_2O)	3444, 2938, 2878, 1638, 1572, 1484, 1424, 1406, 1361, 1317, 1202, 1094, 1015, 946	0.91(3H, t), 1.23-1.38(2H, m), 1.40-1.51(2H, m), 1.64-1.95 (2H, m), 1.98-2.38(4H, m), 2.12(3H, s), 2.18(3H, s), 2.24 & 2.25(3H, each s), 2.75 & 2.86(3H, each s), 2.93-3.06(2H, m), 3.28 & 4.39-4.59(2H, m), 3.49(2H, m), 3.69 & 3.72(2H, each s), 6.74 & 6.75(1H, each s)
133		pale yellow cryst. (HCl salt) 186-189 (MeOH/Et_2O)	2936, 2726, 1646, 1571, 1486, 1420, 1337, 1306, 1106, 1030, 942, 826	1.47-1.63(2H, m), 1.67-1.81(2H, m), 1.82-2.07(2H, m), 2.11(3H, s), 2.18(3H, s), 2.23 & 2.24(3H, each s), 2.76 & 2.90(3H, each s), 2.99(2H, m), 3.31 & 4.36-4.62(2H, m), 3.47(2H, brs), 3.65(2H, s), 3.68 & 3.71(2H, each s), 6.73 & 6.74(1H, each s), 7.42-7.52(3H, m), 7.73-7.80 (1H, m), 7.81(3H, m)

No.	Chemical Structure	Properties m. p. (℃) (solvent)	IR (KBr): cm^{-1} (HCl salt)	^1H-NMR ($CDCl_3$)
134		colorless cryst. (HCl salt) 160-163 (MeOH/Et_2O)	2942, 2818, 1634, 1488, 1430, 1332, 1273, 1252, 1168, 1128, 1073, 1023, 816	1.45-1.88(4H, m), 2.12(3H, s), 2.17 & 2.18(3H, each s), 2.25(3H, s), 2.77 &2.89(3H, each s), 3.17 & 4.47(1H, m), 3.38-3.85(4H, m), 3.71 & 3.75(2H, each s), 4.79(2H, m), 6.72 & 6.74(1H, each s), 7.59(2H, m), 7.69(2H, m)
135		pale yellow cryst. (HCl salt) 156-158 (MeOH/Et_2O)	3440, 2954, 1618, 1576, 1448, 1371, 1323, 1280, 1129, 1115, 1021, 790	1.44-1.84(4H, m), 2.21(3H, s), 2.26(3H, s), 2.27(3H, s), 2.72-2.93(2H, m), 2.78 & 2.79(3H, each s), 2.81(6H, s) 3.13 & 4.57(1H, m), 3.40-3.64(2H, brs), 3.68-3.93(2H, m), 4.78(2H, m), 6.78(1H, s), 7.41(5H, brs)
136		pale brown amorphous	3426, 2940, 1654, 1514, 1454, 1415, 1390, 1310, 1246, 1221, 1101	HCl salt in DMSO-d_6: 1.71 & 1.90(2H, m), 2.09 & 2.11(3H, each s), 2.18(3H, s), 2.28(2H, m), 2.79 & 2.93(3H, each s), 3.07-3.17(4H, m), 3.26(2H, m), 3.57-3.63(2H, m), 3.97 & 4.08(2H, each s), 4.60(1H, m), 6.65 & 6.69(1H, each s), 7.03(1H, s), 7.27-7.35(5H, m)
137		pale brown amorphous	3426, 2940, 1639, 1514, 1498, 1461, 1414, 1303, 1248, 1095, 1030	HCl salt in DMSO-d_6: 1.09-1.17(2H, m), 1.45(1H, m), 1.69 & 1.89(2H, m), 2.11(3H, s), 2.17 & 2.18(3H, each s) 2.24-2.40(3H, m), 2.78 & 2.92(3H, each s), 3.05-3.17 (4H, m), 3.54(2H, m), 3.96 & 4.07(2H, each s), 4.58(1H, m), 6.65 & 6.68(1H, each s), 7.01(1H, s), 7.17(3H, m), 7.28(2H, m)

No.	Chemical Structure	Properties m. p. (°C) (solvent)	IR (KBr): cm^{-1} (HCl salt)	^{1}H-NMR (DMSO-D_6): HCl salt
138		pale yellow cryst. (HCl salt) 206-210 (MeOH/Et_2O)	3378, 2936, 2630, 1641, 1518, 1413, 1308, 1202, 1098, 1074, 755	1.67-1.97(2H, m), 2.20(2H, m), 2.78 & 2.90(3H, each s), 3.08(4H, m), 3.28(2H, m), 3.40-3.57 & 4.56(1H, m), 3.65(2H, m), 3.95 & 4.05(2H, each s), 6.79 & 6.84(1H, each s), 7.14 & 7.15(1H, each s), 7.21-7.41(5H, m), 10.43(1H, brs)
139		pale brown powder 178-181 (MeOH/ iso-Pr_2O)	3444, 2942, 2596, 1692, 1637, 1556, 1488, 1448, 1405, 1346, 1302, 1153,	1.72 & 1.86(2H, m), 2.18(2H, m), 2.78 & 2.80(3H, each s), 3.29(2H, m), 3.59(2H, m), 4.09 & 4.16(4H, each s), 4.58 (1H, m), 7.08-7.15(3H, m), 7.36(2H, t), 7.62(2H, m)

The effects, such as cytoprotective effect against glutamate induced cell death using neuron of cerebral cortex, calbindin D28Kd inducing effect by the western blot technique, and cerebral edema suppressing effect of aminophenoxyacetic acid derivatives, of the formula (I) have been evaluated by following biological testing methods.

Biological test 1: Cytoprotective effet agaist glutamate induced cell death

In accordance with the method of M. P. Mattoson [M. P. Mattoson, *Brain Res. Rev.*, 13, 179 (1988)], brain of 18-days fetus rats of Wister strain were taken out. Then, cells of cerebral cortex (4×10^5 cells / ml) were seeded on poly-L-lysine coated 96 wells flat bottom plate (Sumitomo Bakelite Co., Ltd.) in concentration of 4×10^4 cells / each well. After 48 hours of incubation, 1 μM of test compounds were added, then after further 24 hours, 1 mM of glutamate were further added for inducing the cell injury. 12 hours after adding glutamate, MTT [3-(4,5-dimethylthiazol)-2,5-diphenyltetrazolium bromide] was added and incubated for 6 hours.

After incubation, 200 μl of dimethy sulfoxide was added to each wells, and the amounts of reduced MTT were colorimetrically analyzed by Micro ELISA Reader using 570 nm of main-wavelength and 650 nm of sub-wavelength.

The effect of the test compounds was determined as the survival rate of living cells (%) according to the following equation:

Survival rate of living cells (%) =
[(test compound group - glutamate treated group) ÷
(control group - glutamate treated group)] x 100

That is, the survival rate of living cells after incubation of the control group was converted to 100 %, and the survival rata of living cells of the tested compounds was shown in Table II.

Table II

Compound No.	Survival Rate (%) (Compound: 1 μM)	Compound No.	Survival Rate (%) (Compound: 1 μM)
38	114	94	198
40	108	95	61
41	86	96	91
42	131	97	119
44	93	98	120
45	190	99	151
46	101	100	138
48	207	101	138
49	193	102	89
50	54	103	180
53	144	104	117
60	60	105	86
61	58	106	151
62	63	107	227
65	73	109	76
66	60	110	61
67	69	111	84
68	75	112	76
69	68	113	74
70	88	114	50
71	89	116	59
74	87	119	115
75	96	120	88
76	106	121	82
77	111	124	86
78	96	125	52
79	79	126	47
80	99	127	72
81	97	128	81

82	149	129	64
83	65	130	60
84	87	131	65
85	98	132	60
86	127	133	101
87	81	134	79
88	81	135	76
89	126	136	81
90	149	137	71
91	203	138	42
92	66	139	53
93	171		

Biological test 2: Calbindin D28Kd inducing effect

In accordance with the method of M. P. Mattoson [M. P. Mattoson, *Brain Res. Rev.*, 13, 179 (1988)], brain of 18-days fetus rats of Wister strain were taken out. Then, cells of cerebral cortex (5,500 cells / mm^2) were seeded on poly-L-lysine coated 6 wells plate (Falcon) (3.5 mm, Sumilon) and incubated for 7 days.

Test compounds were added on culture day 5, and after 7 days of incubation, the protein was extracted with homogenized buffer solution [containing 20 mM of Tris-HCl (pH=7.4), 1 mM of EDTA, and 0.1 mM of phenylmethylsulfonyl fluoride].

The effect of the test compounds was determined by the western blot technique using polyclonal anti calbindine D28K (Swant Co., Ltd.) as antibody.

Table III shows the test results. In the table, the amount of induced calbindine D28Kd of the control group (none-treated group) was indicated as 100 percents.

Table III:

Compound No.	Amount of induced Calbindine D28Kd (% vs. control) (Compound: 1 μM)
29	122
40	150
111	167
128	171
Control	100

Biological test 3: Cerebral edema suppressing effect

8-week-old rats of slc : Wister strain were used. Rats were anesthetized by intraperitoneal administration of 50 mg/kg of Nembutal (Trade Name), and then, fixed on brain fixactor. The sterile metal screw (3.75 mm in length / 1.0 mm in diameter / 0.75 mm in length of screw thread) was plugged in the 1.5mm right and 0.8 mm rear side of the bregma to press frontparietal cortex organ to cause brain injury.

6 days after the operation, the whole brain was taken out and right cerebral hemisphere (injured side) was isolated. After measurement of the wet weight of the cerebral hemisphere, it was dried at 110 °C for 24 hours on aluminum foil. The dry weight of the cerebral hemisphere was measured, and the water content was calculated by using the following formula:

Water content (%) = [(wet weight of hemisphere - dry weight of hemisphere) / wet weight of hemisphere] x 100

The test compounds were intravenously administered just after the operation via tail vein of the rats.

Table IV shows the test results.

Table IV:

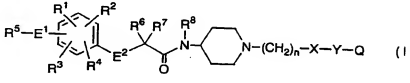
Compound No. (administration amount)	Cerebral edema suppressing rate (%)
29 (3 mg/kg)	30.9
40 (1 mg/kg)	31.1
40 (3 mg/kg)	20.5
42 (1 mg/kg)	24.5
42 (3 mg/kg)	31.0
104 (3 mg/kg)	18.9
105 (3 mg/kg)	23.2
108 (3 mg/kg)	20.3
109 (3 mg/kg)	24.7
111 (3 mg/kg)	25.0
112 (3 mg/kg)	20.7
113 (3 mg/kg)	20.0
119 (1 mg/kg)	21.6
128 (3 mg/kg)	20.3
132 (1 mg/kg)	30.4
134 (1 mg/kg)	27.9
134 (3 mg/kg)	35.0

INDUSTRIAL APPLICABILITY

As described above, the present invention provides lower molecular weight compounds, especially aminophenoxyacetic acid derivatives of the formula (I), which is capable of inducing the calbindin D28Kd, one of Ca^{2+}-binding proteins, and can be easily administrated. Since the induction of calbindin D28Kd caused by the administration of the compound provided by the present invention cause neuroprotective effect and cerebral functional and organic disorder improving and treating effect, it can be understood that the agent of the present invention is highly applicable in pharmaceutical field.

CLAIMS

1. An aminophenoxyacetic acid derivative represented by the following formula (I):



(I)

wherein:

R^1, R^2, R^3 and R^4 are, independent from each other, hydrogen atom; halogen atom; hydroxy group; alkoxy group which may be substituted; alkyl group which may be substituted; aryl group which may be substituted; or aralkyl group which may be substituted;

R^5, R^6, R^7 and R^8 are, independent from each other, hydrogen atom; alkyl group which may be substituted; aryl group which may be substituted; or aralkyl group which may be substituted;

E^1 is oxygen atom; sulfur atom; or group $-NR^9-$ (in which, R^9 is hydrogen atom; alkyl group which may be substituted; aryl group which may be substituted; or aralkyl group which may be substituted);

E^2 is oxygen atom; sulfur atom; or group $-NR^{10}-$ (in which, R^{10} is hydrogen atom; alkyl group which may be substituted; aryl group which may be substituted; or aralkyl group which may be substituted);

n is 0 to 5 (provided that n=0, one of the groups of X and Y may be connecting bond but both of the groups of X and Y do not represent connecting bond at the same time);

X and Y are, independent from each other, connecting bond; alkylene group which may be substituted by hydroxyl group; cyclo-

alkylene group; alkenylene group which may be substituted by lower alkyl group; -NHCO-; -CONH- or -SO_2-;

Q is hydrogen atom; phenyl group which may be substituted; phenoxy group which may be substituted; benzoyl group which may be substituted; pyridyl group which may be substituted; quinolyl group which may be substituted; isoquinolyl group which may be substituted; or benzimidazolyl group which may be substituted;

(provided that both E^1 and E^2 do not represent oxygen atom or sulfur atom at the same time, and in the case of E^1 is nitrogen atom and E^2 is oxygen atom, or in the case of E^1 is oxygen atom and E^2 is nitrogen atom, all of the groups of R^1, R^2, R^3 and R^4 do not represent methyl group at the same time),

or a pharmaceutically acceptable salt thereof.

2 The aminophenoxyacetic acid derivative of formula (I) claimed in claim 1, wherein R^1, R^2, R^3 and R^4 are, independent from each other, hydrogen atom; halogen atom; alkoxy group; or alkyl group which may be substituted; R^5 is hydrogen or alkyl group which may be substituted; E^1 is -NH-; and E^2 is oxygen atom, or a pharmaceutically acceptable salts thereof.

3 The aminophenoxyacetic acid derivative of formula (I) claimed in claim 1, wherein E^1 is -NH-; E^2 is oxygen atom; X is connecting bond; Q is phenyl group which may be substituted, or a pharmaceutically acceptable salt thereof.

4 The aminophenoxyacetic acid derivative of formula (I) claimed in claim 1, wherein E^1 and E^2 are -NH-; X and Y are connecting bond; Q is phenyl group which may be substituted, or a pharmaceutically acceptable salt thereof.

5. Medicament containing aminophenoxyacetic acid derivative

or a pharmaceutically acceptable salt thereof represented by the formula (I) claimed in claim 1, as an active ingredient.

6. Medicament containing aminophenoxyacetic acid derivative or a pharmaceutically acceptable salt thereof according to any one of claims 2 to 4, as an active ingredient.

7. Calbindin D28Kd, which is Ca^{2+}-binding protein, inducer containing aminophenoxyacetic acid derivative or a pharmaceutically acceptable salt thereof represented by the formula (I) claimed in claim 1, as an active ingredient.

8. Calbindin D28Kd, which is Ca^{2+}-binding protein, inducer containing aminophenoxyacetic acid derivative or a pharmaceutically acceptable salt thereof according to any one of claims 2 to 4, as an active ingredient.

9. A cerebral functional and organic function improving or therapeutic agent containing aminophenoxyacetic acid derivative or a pharmaceutically acceptable salt thereof represented by the formula (I) claimed in claim 1, as an active ingredient.

10. A cerebral functional and organic function improving or therapeutic agent containing aminophenoxyacetic acid derivative or a pharmaceutically acceptable salt thereof according to any one of claims 2 to 4, as an active ingredient.

11. A method for selecting neuroprotective compound based on the measurement of amounts of calbindin D28Kd induced thereby.

12. Neuroprotevive compounds selected by the method according to claim 11.

13. Medicament containing neuroprotective compounds according to claim 12.

14. Medicamnet containing compounds having neuroprotective effect by inducing the calbindin D28Kd, which is Ca^{2+}-binding protein.

15. The medicament according to claim 14 for treating or improving of functional disorders in the brain due to various ischemic disorders such as sequelae of cerebral infarction, sequelae of intracerebral hemorrhage, sequelae of cerebral arteriosclerosis and so on, as well as organic disorders in the brain such as senile dementia, sequelae of head trauma, sequelae of surgical brain operation, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and so on.

16. The medicament according to claim 14 or 15, wherein the neuroprotective compound is the aminophenoxyacetic acid derivative of formula (I) in claimed in claim 1.

INTERNATIONAL SEARCH REPORT

Inter...tional Application No
PCT/JP 99/05658

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4468 C07D211/58 A61K31/4545 C07D401/06 C07D401/12
G01N33/15

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 318 029 A (EISAI CO LTD) 31 May 1989 (1989-05-31) page 3, line 7 - line 27; claims	1-10
A	EP 0 481 299 A (BASF AG) 22 April 1992 (1992-04-22) page 6, line 48 - line 53	1-10
A	WO 93 25528 A (RICHTER GEDEON VEGYESZET ;DOMANY GYORGY (HU); BARTANE SZALAI GIZE) 23 December 1993 (1993-12-23)	1-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 January 2000	20/01/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	De Jong, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter...ational Application No
PCT/JP 99/05658

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	GRASBON-FRODL, E. M. ET AL: "Phenotypic development of the human embryonic striatal primordium: a stud of cultured and grafted neurons from the lateral and medial ganglionic eminences" NEUROSCIENCE (OXFORD) (1996), 73(1), 171-183 , XP002126321 page 177, right-hand column	11
A	LIU, FU CHIN ET AL: "Influence of mesostriatal afferents on the development and transmitter regulation of intrastriatal grafts derived from embryonic striatal primordia" J. NEUROSCI. (1992), 12(11), 4281-97 , XP002126322 page 4285, right-hand column	11
A	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US MATTSON, MARK P. ET AL: "Evidence for calcium-reducing and excito-protective roles for the calcium-binding protein calbindin-D28k in cultured hippocampal neurons" retrieved from STN Database accession no. 114:161473 XP002126323 abstract & NEURON (1991), 6(1), 41-51 , cited in the application	11
A	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US HUGON, J. ET AL: "The presence of calbindin in rat cortical neurons protects in vitro from oxidative stress" retrieved from STN Database accession no. 124:227945 XP002126325 abstract & BRAIN RES. (1996), 707(2), 288-92 ,	11
P,X	EP 0 913 393 A (SSP CO LTD) 6 May 1999 (1999-05-06) claim 1	1

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 99/05658

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 12-16
because they relate to parts of the international Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 12-16

Present claims 12-16 relate to compounds/medicaments defined by reference to a desirable characteristic or property, namely their ability to increase the amount of calbindin D28Kd.

Claims 12-16 cover all compounds/medicaments having this property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds/medicaments. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds/medicaments by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to compounds according to claim 1 and medicaments containing these compounds.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte...ational Application No
PCT/JP 99/05658

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		DE 3854991 D	21-03-1996
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EP 0481299 A	22-04-1992	DE 4032766 A	30-04-1992
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